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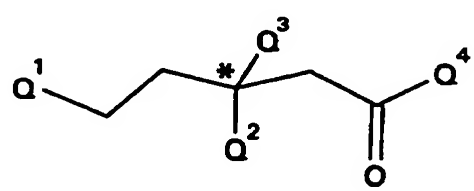
(54) Title: 5-(4-SUBST.-PIPERIDINYL-1)-3-ARYL-PENTANOIC ACID DERIVATIVES AS TACHYKININ RECEPTOR ANTAGONIST

(57) Abstract

Compounds of formula (I), wherein Q^1, Q^2, Q^3 and Q^4 have any of the meanings given in the specification, their N-oxided, and their pharmaceutically acceptable salts are nonpeptide antagonists of SP and NKA, useful for the treatment of asthma, etc. Also disclosed are pharmaceutical compositions, processes for preparing the compounds of formula (I) and intermediates.



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5-(4-SUBST.-PIPERIDINYL-1)-3-ARYL-PENTANOIC ACID DERIVATIVES AS TACHYKININ RECEPTOR ANTAGONIST

This invention concerns novel substituted 5-(heterocyclic)valeryl derivatives which antagonize the pharmacological actions of the endogenous neuropeptide tachykinins known as neurokinins, particularly at the neurokinin 1 (NK1) and the neurokinin 2 (NK2) receptors. The novel 5-(heterocyclic)valeryl derivatives are useful whenever such antagonism is desired. Thus, such compounds may be of value in the treatment of those diseases in which the NK1 and/or NK2 receptor is implicated, for example, in the treatment of asthma and related conditions. The invention also provides pharmaceutical compositions containing the novel 5-(heterocyclic)valeryl derivatives for use in such treatment, methods for their use, and processes and intermediates for the manufacture of the novel 5-(heterocyclic)valeryl derivatives.

The mammalian neurokinins comprise a class of peptide neurotransmitters which are found in the peripheral and central nervous systems. The three principal neurokinins are SP (SP), Neurokinin A (NKA) and Neurokinin B (NKB). There are also N-terminally extended forms of at least NKA. At least three receptor types are known for the three principal neurokinins. Based upon their relative selectivities favoring the neurokinin agonists SP, NKA and NKB, the receptors are classifed as neurokinin 1 (NK1), neurokinin 2 (NK2) and neurokinin 3 (NK3) receptors, respectively. In the periphery, SP and NKA are localized in C-afferent sensory neurons, which neurons are characterized by non-myelinated nerve endings known as C-fibers, and are released by selective depolarization of these neurons, or selective stimulation of the C-fibers. C-Fibers are located in the airway epithelium, and the tachykinins are known to cause profound effects which clearly parallel many of the symptoms observed in asthmatics. The effects of release or introduction of tachykinins in mammalian airways include bronchoconstriction, increased microvascular permeability, vasodilation, increased mucus secretion and activation of mast cells. Thus, the tachykinins are implicated in the pathophysiology and airway hyperresponsiveness observed in asthmatics; and blockade of the action of released tachykinins may be useful in the treatment of asthma and related conditions. A cyclopeptide antagonists (FK-224) selective for both NK1 and NK2 receptors has demonstrated clinical efficacy in human patients

suffering from asthma and chronic bronchitis. M. Ichinose, et al., Lancet, 1992, 340, 1248. Nonpeptidic tachykinin antagonists have been reported, for example in European Patent Application, Publication Number (EPA) 428434, EPA 474561, EPA 512901, EPA 512902, EPA 515240 and EPA 559538, as well as in WO 94/10146, EPA 0625509, EPA 0630887, WO 95/05377, WO 95/12577, WO 95/15961, EPA 680962, and WO 95/16682. We have discovered a series of non-peptidic antagonists of the NK1 and NK2 receptors, and this is the basis for our invention.

According to the invention, there is provided a Compound of the invention which is a compound of formula I (formula set out hereinbelow following the Examples, together with other formulae denoted by Roman numerals) wherein

Q^1 is a radical selected from the group of radicals of formulae Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ij, Ik, Im, In, Ip, Iq, Ir, Iu, Iv, Iw and Ix wherein

for a radical of formula Ia, Z^a is nitrogen or a group CR^{ad} in which R^{ad} is hydrogen or R^{ad} together with R^{ac} and the existing carbon to carbon bond forms a double bond; R^{aa} is Ar or Het; R^{ab} is hydrogen and R^{ac} is hydrogen or hydroxy or R^{ac} together with R^{ad} and the existing carbon to carbon bond forms a double bond, or R^{ac} and R^{ad} together form a diradical $-(CH_2)_j-$ in which j is an integer from 1 to 5; or R^{ab} and R^{ac} together form a diradical $-(CH_2)_k-$ in which k is an integer from 2 to 6, or R^{ab} and R^{ac} together are oxo or dialkylaminoalkyloxyimino of formula $=N-O-(CH_2)_q-NR^{ae}R^{af}$ in which q is the integer 2 or 3 and R^{ae} and R^{af} are independently hydrogen or (1-4C)alkyl, or the radical $NR^{ae}R^{af}$ is pyrrolidino, piperidino or morpholino;

for a radical of formula Ib, Z^b is a substituted imino group $R^{ba}N$ or $R^{ba}CH_2N$ in which R^{ba} is (3-7C)cycloakyl, Ar, Het, Ar(carbonyl), Het(carbonyl), $CH_2\,NR^{be}R^{bf}$, $C(=O)NR^{be}R^{bf}$, $CH_2C(=O)NR^{be}R^{bf}$; or Z^b is a disubstituted methylene group $R^{bb}(CH_2)_p-C-R^{bc}$ in which R^{bb} is Ar or Het; p is the integer 0 or 1; and R^{bc} is hydrogen, hydroxy, (1-4C)alkoxy, (1-4C)alkanoyloxy, $COOR^{bd}$ (wherein R^{bd} is hydrogen or (1-3C)alkyl), cyano, $CH_2\,NR^{be}R^{bf}$, $C(=O)NR^{be}R^{bf}$, $NR^{be}R^{bf}$ or SR^{bg} in which R^{be} and R^{bf} are independently hydrogen, (1-4C)alkyl, (1-4C)hydroxyalkyl or (1-4C)alkanoyl, or the

radical $NR^{be}R^{bf}$ is pyrrolidino, piperidino or morpholino; and R^{bg} is hydrogen or (1-4C)alkyl; or R^{bc} forms a double bond with the carbon atom to which it is bonded and with the adjacent carbon atom in the piperidine ring; or Z^b is a disubstituted methylene group $R^{bh}CR^{bi}$ which forms a spirocyclic ring wherein R^{bh} is phenyl which is joined by an ortho-substituent diradical X^b to R^{bi} in which the phenyl R^{bh} may bear a further substituent selected from halo, (1-3C)alkyl, (1-3C)alkoxy, hydroxy, (1-3C)alkylthio, (1-3C)alkylsulfinyl and (1-3C)alkylsulfonyl; the diradical X^b is methylene, carbonyl or sulfonyl; and R^{bi} is oxy or imino of formula $-NR^{bj}-$ in which R^{bj} is hydrogen or (1-3C)alkyl;

for a radical of formula Ic, R^{ca} is Ar or Het; and Z^c is oxo, thio, sulfinyl, sulfonyl or imino of formula $-NR^{cb}-$ in which R^{cb} is (1-3C)alkyl or $R^{cc}R^{cd}N-(CH_2)_q-$ in which q is the integer 2 or 3 and in which R^{cc} and R^{cd} are independently hydrogen or (1-3C)alkyl or the radical $R^{cc}R^{cd}N$ is pyrrolidino, piperidino or morpholino;

for a radical of formula Id, R^{da} is 1, 2 or 3;

for a radical of formula Ie, J^e is oxygen, sulfur or NR^{ea} in which R^{ea} is hydrogen or (1-3C)alkyl; R^{eb} is hydrogen, (1-6C)alkyl which may bear a hydroxy substituent and/or one to three fluoro substituents, (3-6C)alkenyl (in which a vinyl carbon is not bound to nitrogen), 2-hydroxyethyl, (3-7C)cyloalkyl, Ar or Het; R^{ec} is hydrogen, (1-6C)alkyl which may bear a hydroxy substituent and/or one to three fluoro substituents, (3-6C)cycloalkyl, (1-5C)alkoxy (only when J^e is oxygen), (3-6C)cycloalkoxy (only when J^e is oxygen), or an amino group of formula $NR^{ed}R^{ee}$ containing zero to seven carbon atoms in which each of R^{ed} and R^{ee} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{ed}R^{ee}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl group may bear a (1-3C)alkyl substituent at the 4-position);

for a radical of formula If, J^f is oxygen, sulfur or NR^{fa} in which R^{fa} is hydrogen or (1-3C)alkyl; L^f is a divalent hydrocarbon group in which the 1-position is bound to the carbon bearing the group J^f, the divalent group L^f being selected from trimethylene, cis-propenylene, tetramethylene, cis-butenylene, cis-but-3-enylene, cis,cis-butadienylene,

pentamethylene and cis-pentenylene which divalent group L^f itself may bear one or two methyl substituents;

for a radical of formula Ig, Z^g is (1-8C)alkyl or (3-8C)cycloalkyl which may bear one or more substituents selected from the group consisting of halo, (3-6C)cycloalkyl, cyano, nitro, hydroxy, (1-4C)alkoxy, (1-5C)alkanoyloxy, aroyl, heteroaroyl, oxo, imino (which may bear a (1-6C)alkyl, (3-6C)cycloalkyl, (1-5C)alkanoyl or aroyl substituent), hydroxyimino (which hydroxyimino may bear a (1-4C)alkyl or a phenyl substituent on the oxygen), an amino group of formula $NR^{ga}R^{gb}$, an amino group of formula $NR^{gc}R^{gd}$, an amidino group of formula $C(=NR^{gg})NR^{ge}R^{gf}$, and a carbamoyl group of formula $CON(OR^{gh})R^{gi}$, but excluding any radical wherein a hydroxy and an oxo substituent together form a carboxy group, wherein an amino group of formula $NR^{ga}R^{gb}$ contains zero to seven carbon atoms and each of R^{ga} and R^{gb} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{ga}R^{gb}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent group at the 4-position); and wherein R^{gc} is hydrogen or (1-3C)alkyl and R^{gd} is (1-5C)alkanoyl, aroyl or heteroaroyl; or R^{gd} is a group of formula $C(=J^g)NR^{ge}R^{gf}$ in which J^g is oxygen, sulfur, NR^{gg} or CHR^{gj}; and wherein the amino group $NR^{ge}R^{gf}$ contains zero to seven carbon atoms and each of R^{ge} and R^{gf} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{ge}R^{gf}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position) or R^{ge} is hydrogen or (1-4C)alkyl and R^{gf} together with R^{gg} forms an ethylene or trimethylene group; R^{gg} is hydrogen, (1-4C)alkyl or together with R^{gf} forms an ethylene or trimethylene group; R^{gj} is cyano, nitro or SO_2R^{gk} and R^{gk} is (1-4C)alkyl or phenyl; R^{gh} and R^{gi} are independently (1-3C)alkyl; and in which a cyclic group which is a substituent on Z^g or formed by substitution on Z^g may bear one or more (1-3C)alkyl groups on carbon as further substituents; and in which any aryl or heteroaryl group which is a part of the group Z^g may bear one or more halo, (1-4C)alkyl, (1-4C)alkoxy, cyano, trifluoromethyl or nitro substituents;

for a radical of formula Ih, G^h denotes a single bond, a double bond or a divalent hydrocarbon radical; J^h denotes a radical joined to the ring by a single bond if G^h denotes a

double bond or, otherwise, a radical joined by a double bond; M^h denotes a heteroatom, a substituted heteroatom, or a single bond; and L^h denotes a hydrocarbon radical in which the 1-position is attached to M^h; wherein the values of G^h, J^h, M^h and L^h are selected from

(a) G^h is a single bond; J^h is oxo or thioxo; M^h is oxy, thio or NR^{ha}; and L^h is L^{ha};

(b) G^h is a single bond; J^h is NR^{hb}; M^h is NR^{ha}; and L^h is L^{ha};

(c) G^h is a double bond, J^h is OR^{ha}, SR^{ha} or $NR^{hc}R^{hd}$; M^h is nitrogen; and L^h is L^{ha};

(d) G^h is methylene which may bear one or two methyl substituents; J^h is oxo, thioxo or NR^{he}; M^h is oxy, thio, sulfinyl, sulfonyl or NR^{ha}; and L^h is L^{hb};

(e) G^h is a single bond; J^h is oxo, thioxo or NR^{he}; M^h is nitrogen; and L^h is L^{hc};

(f) G^h is methine, which may bear a (1-3C)alkyl substituent; J^h is oxo, thioxo or NR^{he}; M^h is nitrogen; and L^h is L^{hd};

(g) G^h is cis-vinylene, which may bear one or two methyl substituents; J^h is oxo, thioxo, or NR^{he}; M^h is nitrogen; and L^h is L^{he}; and

(h) G^h is a single bond; J^h is oxo or thioxo; M^h is a single bond; and L^h is L^{hf};

wherein

R^{ha} is hydrogen or (1-3C)alkyl; R^{hb} is hydrogen, (1-3C)alkyl, cyano, (1-3C)alkylsulfonyl or nitro; R^{hc} and R^{hd} are independently hydrogen or (1-3C)alkyl or the radical $NR^{hc}R^{hd}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{he} is hydrogen or (1-3C)alkyl; L^{ha} is ethylene, cis-vinylene, trimethylene or tetramethylene which radical L^{ha} itself may bear one or two methyl substituents; L^{hb} is ethylene or trimethylene which radical L^{hb} itself may bear one or two methyl substituents; L^{hc} is prop-2-en-1-yliden-3-yl, which radical L^{hc} itself may bear one or two methyl substituents; L^{hd} is cis-vinylene, which radical L^{hd} itself may bear one or two methyl substituents; L^{he} is

methine, which radical L^{he} itself may bear a (1-3C)alkyl substituent; and L^{hf} is 4-oxabutan-1,4-diyl;

for a radical of formula Ij, X^j is (1-6C)alkyl, $-CH_2OR^{ja}$, $-CH_2SR^{ja}$, $-CH_2S(O)R^{jg}$, $-CH_2S(O)_2R^{jg}$, $-COR^{ja}$, $-COOR^{ja}$, $-C(=J^{ja})NR^{jb}R^{jc}$, $-C(R^{ja})(OR^{jd})(OR^{je})$, $-CH_2N(R^{ja})C(=J^{ja})R^{jf}$, $-CH_2N(R^{ja})COOR^{jg}$ or $-CH_2N(R^{ja})C(=J^{ja})NR^{jb}R^{jc}$;

B^j is a direct bond and L^j is a hydrocarbon chain in which the 1-position is bound to B^j and L^j is selected from trimethylene, tetramethylene, cis-1-butenylene and cis,cis-butadienylene; or B^j is $N(R^{jh})$ and L^j is a hydrocarbon chain selected from ethylene, trimethylene and cis-vinylene; or B^j is N and L^j is a hydrocarbon chain in which the 1-position is bound to B^j and L^j is cis,cis-prop-2-en-1-ylidin-3-yl; J^j and J^{ja} are independently oxygen or sulfur; R^{ja}, R^{jf} and R^{jh} are independently hydrogen or (1-6C)alkyl; R^{jb} and R^{jc} are independently hydrogen or (1-6C)alkyl; or the radical $NR^{jb}R^{jc}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{jd} and R^{je} are independently (1-3C)alkyl or together form a divalent hydrocarbon chain selected from ethylene and trimethylene; R^{jg} is (1-6C)alkyl; wherein any (1-6C)alkyl radical in a portion of X^j may substituted by one or two substituents selected from hydroxy, (1-3C)alkoxy, (1-3C)acyloxy, (1-3C)alkoxycarbonyl, $NR^{jh}R^{jj}$, and $C(=O)NR^{jh}R^{jj}$, wherein R^{jh} and R^{jj} are independently hydrogen, (1-4C)alkyl, (1-4C)hydroxyalkyl or (1-4C)alkanoyl, or the group $NR^{jh}R^{jj}$ is pyrrolidino, piperidino or morpholino; and

for a radical of formula Ik, Z^k is a nitrogen linked radical of formula II wherein E^1, E^2, E^3 and E^4 form a divalent four membered chain ($-E^1=E^2-E^3=E^4-$) in which each of E^1, E^2, E^3 and E^4 is methine; or in which one or two of E^1, E^2, E^3 and E^4 is nitrogen and the remaining E^1, E^2, E^3 and E^4 are methine; and further wherein one or more of E^1, E^2, E^3 and E^4 which is methine may bear a halo, (1-3C)alkyl, hydroxy, (1-3C)alkoxy, (1-3C)alkylthio, (1-3C)alkylsulfinyl or (1-3C)alkylsulfonyl substituent; and wherein the radicals F^k, G^k, and $I^k(X^k)$ are selected from

(a) G^k is a direct bond, $I^k(X^k)$ is a radical having the formula $=C(Z^k)-$ and F^k is a radical selected from -CH= and -N=;

(b) G^k is a direct bond, $I^k(X^k)$ is a radical having the formula $-C(=J^k)-$ and F^k is a radical selected from $-N(R^{kf})-$, $-CH_2-CH_2-$, -CH=CH-, $-CH_2-N(R^{kf})-$ and -CH=N-;

(c) G^k is a radical having the formula $-CH_2-$, $I^k(X^k)$ is a radical having formula $-C(=J^k)-$ and F^k is selected from $-CH_2-$ and $-N(R^{kf})-$; and

(d) G^k is selected from $-CH_2-$, $-CH_2-CH_2-$, -CH=CH- and -N=CH-, $I^k(X^k)$ is a radical having the formula $-C(=J^k)-$ and F^k is a direct bond; wherein

J^k is oxygen or sulfur; Z^k is $-OR^{ka}$, $-SR^{ka}$, $-COR^{ka}$, $-COOR^{ka}$, $-C(=J^{ka})NR^{kb}R^{kc}$ or $-C(R^{ka})(OR^{kd})(OR^{ke})$; J^{ka} is oxygen or sulfur; R^{ka} and R^{kf} are independently hydrogen or (1-6C)alkyl; R^{kb} and R^{kc} are independently hydrogen or (1-6C)alkyl; or the radical $NR^{kb}R^{kc}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{kd} and R^{ke} are independently (1-3C)alkyl or R^{kd} and R^{ke} together form ethylene or trimethylene; or Z^k is an imido radical selected from phthalimido, succinimido, maleimido, glutarimido, and 3-oxa-, 3-thia- and 3-azaglutarimido, in which the imido radical may bear one or more (1-3C)alkyl substituents and, in addition, the aromatic portion of the phthalimido may bear one or more halo, hydroxy or (1-3C)alkoxy substituents;

for a radical of formula Im, R^{ma} and R^{mb} are Ar or Het and R^{mc} is selected from hydroxy, (1-3C)alkoxy, and (1-3C)acyloxy; or R^{ma} is (Ar)oxy, or (Het)oxy, and R^{mb} and R^{mc} are hydrogen;

for a radical of formula In, X^n is selected from hydrogen, hydroxy, (1-3C)alkoxy and (1-3C)acyloxy;

for a radical of formula Ip, R^{pa} and R^{pb} are independently selected from hydrogen, hydroxy, (1-3C)alkoxy, (1-3C)acyloxy, halo, cyano, and trifluoromethyl;

for a radical of formula Iq, R^{qa}-R^{qd} are are independently selected from hydrogen, hydroxy, (1-3C)alkoxy, (1-3C)acyloxy, halo, cyano, and trifluoromethyl;

for a radical of formula Iu, Ju is oxygen or sulfur: and R^{ua}-R^{ud} are independently selected from hydrogen, (1-4C)alkyl, (1-4C)hydroxyalkyl and (1-4C)alkanoyl, or the group $NR^{ua}R^{ub}$ or the group $NR^{uc}R^{ud}$ is pyrrolidino, piperidino or morpholino;

for a radical of formula Iw, w is 1, 2, or 3; and wherein

for a radical Q^1, Ar is a phenyl radical or an ortho-fused bicyclic carbocyclic radical of nine of ten ring atoms in which at least one ring is aromatic, which radical Ar may be unsubstituted or may bear one or more substituents selected from halo, cyano, trifluoromethyl, (1-4C)alkyl, (1-4C)alkoxy, methylenedioxy, hydroxy, mercapto, $-S(O)_nR^{xa}$, (1-5C)alkanoyl, (1-5C)alkanoyloxy, nitro, $NR^{xb}R^{xc}$, $NR^{xd}R^{xe}$, $C(=NR^{xf})NR^{xg}R^{xh}$, $CONR^{xb}R^{xc}$ and $COOR^{xj}$ wherein n is the integer 0, 1, or 2; R^{xa} is (1-6C)alkyl, (3-6C)cycloalkyl or phenyl (which phenyl may bear a halo, trifluoromethyl, (1-3C)alkyl or (1-3C)alkoxy substitutent); the radical $NR^{xb}R^{xc}$ contains zero to seven carbons and each of R^{xb} and R^{xc} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{xb}R^{xc}$ is pyrrolidino, piperidino, morpholino, thiomorpholine (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); and wherein R^{xd} is hydrogen or (1-4C)alkyl and R^{xe} is (1-5C)alkanoyl, benzoyl; or a group of formula $C(=J^x)NR^{xg}R^{xh}$ in which J^x is oxygen, sulfur, NR^{xf} or CHR^{xi}; R^{xf} is hydrogen, (1-5C)alkyl or together with R^{xg} forms an ethylene or trimethylene diradical, the radical $NR^{xg}R^{xh}$ contains zero to 7 carbons and each of R^{xg} amd R^{xh} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{xg}R^{xh}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); or R^{xg} together with R^{xf} forms an ethylene or trimethylene diradical and R^{xh} is hydrogen or (1-5C)alkyl; R^{xi} is cyano, nitro, (1-5C)alkylsulfonyl or phenylsulfonyl; and R^{xj} is hydrogen, (1-5C)alkyl or benzyl; and Het is a radical (or stable N-oxide thereof) attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms selected

from oxygen, sulfur and nitrogen, or an ortho-fused bicyclic heterocycle derived therefrom by fusing a propenylene, trimethylene, tetramethylene or benz-diradical, which radical Het may be unsubstituted or may be substituted on carbon by one or more of the substituents defined above for Ar and may be substituted on nitrogen by (1-3C)alkyl;

Q^2 is phenyl which may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl and methylenedioxy; or Q^2 is thienyl, imidazolyl, benzo[b]thiophenyl or naphthyl any of which may bear a halo substituent; or Q^2 is biphenylyl; or Q^2 is carbon-linked indolyl which may bear a benzyl substituent at the 1-position;

Q^3 is hydrogen, or (1-4C)alkyl; and

Q^4 is $-OR^2$ or $-NR^3R^4$; wherein

R^2 is hydrogen, (1-6C)alkyl, (3-7C)cycloalkyl, aryl(1-3C)alkyl or heteroaryl(1-3C)alkyl, wherein an aryl or heteroaryl group may bear one, two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-S(=O)_2NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, and methylenedioxy, and further wherein any arylethyl, arylpropyl, heteroarylethyl or heteroarylpropyl group may optionally be substituted at the position a to the aryl or heteroaryl group by a group selected from oxo, and $=NOR^{11}$;

R^3 and R^4 are independently selected from hydrogen, (1-8C)alkyl, norbornyl, adamantyl, quinuclidinyl, (1-6C)alkoxy, (3-7C)cycloalkyl, pyrrolidinyl, tetrahydrofuranyl, piperidyl, 1-benzylpiperidyl, 4,5-dihydrothiazolyl, 3,4,5,6-tetrahydrophenyl, fluorenyl, 5-oxo-4,5-dihydropyrazol-3-yl, aryl, heteroaryl, arylsulfinyl, arylsulfonyl, heteroarylsulfinyl, heteroarylsulfonyl, 1-phenyl-4,5-dihydropyrazol-3-yl, 1-benzylpyrrolidin-3-yl, and a radical of formula VII; wherein (1-8C)alkyl may be substituted by one, two, or three substituents selected from, hydroxy, oxo, $=NOR^{11}$, amino, pyrrolidinyl, 1-methylpyrrolidinyl, piperidinyl, (1-3C)alkoxy, (1-4C)alkanoyl, (1-3C)alkoxycarbonyl, (3-7C)cycloalkyl, adamantyl, norbornyl, quinuclidinyl, tetrahydrofuranyl, 4,5-dihydrothiazolyl, 3,4,5,6-tetrahydrophenyl, fluorenyl, 5-oxo-4,5-dihydropyrazol-3-yl, aryl and heteroaryl; and further wherein any aryl or heteroaryl group, or radical of formula VII may bear one two or three

substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, (1-4C)alkanoyl, C(=O)OR5, $-S(=O)_2NR^5R^6$, $-S(=O)NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, and methylenedioxy; provided that R^3 and R^4 are not both selected from (1-6C)alkoxy; or

$-NR^3R^4$ taken together represents a cyclic amino radical selected from piperazinyl, pyrrolidinyl, piperidino, 1,2,3,6-tetrahydropyridyl, 1,2,3,4-tetrahydroquinolyl, and 1,2,3,4-tetrahydroisoquinolyl, which cyclic amino radical may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-4C)alkanoyl, (1-3C)alkyl, cyano, $-S(=O)^2NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, $CH_2N(R^7)C(=O)R^8$, pyrrolidinyl, 2-(thioxo)pyrrolidinyl, piperidinyl, pyridyl, morpholinocarbonyl, piperidinocarbonyl, 2-oxo-benzimidazolidin-1-yl, phenyl, benzyl, acetamidomethyl, and methylenedioxy; wherein any phenyl or phenyl portion of benzyl may optionally bear one, two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, or cyano; or

$-NR^3R^4$ taken together represents an amino radical selected from radicals of formulae VIII, IX, and X.

E is selected from -O-, -S-, $-N(R^{14})-$, -S(=O)- and $-S(O)_2-$;

m is 1 or 2; and

R^5-R^{11} are independently selected from hydrogen and (1-3C)alkyl

or the N-oxide of the nitrogen in Q^1 indicated by Δ in formulae Ia-Ix (or of either basic piperazinyl nitrogen of Q^1 when Z^a is nitrogen);

or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the nitrogen in Q^1 indicated by Δ in formulae Ia-Ix (or either basic piperazinyl nitrogen of Q^1 when Z^a is nitrogen) is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R^1 is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

A particular sub-set of compounds of the invention are compounds of formula I wherein:

Q^1 is a radical selected from the group of radicals of formulae Ia, Ib. Ic, Id, Ie, If, Ig. Ih, Ij and Ik wherein

for a radical of formula Ia. Z^a is nitrogen or a group CR^{ad} in which R^{ad} is hydrogen or R^{ad} together with R^{ac} and the existing carbon to carbon bond forms a double bond: R^{aa} is Ar or Het; R^{ab} is hydrogen and R^{ac} is hydrogen or hydroxy or R^{ac} together with R^{ad} and the existing carbon to carbon bond forms a double bond. or R^{ac} and R^{ad} together form a diradical $-(CH_2)_j-$ in which j is an integer from 1 to 5; or R^{ab} and R^{ac} together form a diradical $-(CH_2)_k-$ in which k is an integer from 2 to 6. or R^{ab} and R^{ac} together are oxo or dialkylaminoalkyloxyimino of formula $=N-O-(CH_2)_q-NR^{ae}R^{af}$ in which q is the integer 2 or 3 and R^{ae} and R^{af} are independently hydrogen or (1-4C)alkyl. or the radical $NR^{ae}R^{af}$ is pyrrolidino, piperidino or morpholino;

for a radical of formula Ib, Z^b is a substituted imino group $R^{ba}N$ or $R^{ba}CH_2N$ in which R^{ba} is (3-7C)cycloakyl, Ar or Het; or Z^b is a disubstituted methylene group $R^{bb}(CH_2)_p-C-R^{bc}$ in which R^{bb} is Ar or Het; p is the integer 0 or 1; and R^{bc} is hydrogen, hydroxy, (1-4C)alkoxy, (1-4C)alkanoyloxy, $COOR^{bd}$ (wherein R^{bd} is hydrogen or (1-3C)alkyl), cyano, $NR^{be}R^{bf}$ or SR^{bg} in which R^{be} and R^{bf} are independently hydrogen, (1-4C)alkyl, (1-4C)hydroxyalkyl or (1-4C)alkanoyl, or the radical $NR^{be}R^{bf}$ is pyrrolidino, piperidino or morpholino; and R^{bg} is hydrogen or (1-4C)alkyl; or R^{bc} forms a double bond with the carbon atom to which it is bonded and with the adjacent carbon atom in the piperidine ring; or Z^b is a disubstituted methylene group $R^{bh}CR^{bi}$ which forms a spirocyclic ring wherein R^{bh} is phenyl which is joined by an ortho-substituent diradical X^b to R^{bi} in which the phenyl R^{bh} may bear a further substituent selected from halo, (1-3C)alkyl, (1-3C)alkoxy, hydroxy, (1-3C)alkylthio, (1-3C)alkylsulfinyl and (1-3C)alkylsulfonyl; the diradical X^b is methylene, carbonyl or sulfonyl; and R^{bi} is oxy or imino of formula $-NR^{bj}-$ in which R^{bj} is hydrogen or (1-3C)alkyl;

for a radical of formula Ic, R^{ca} is Ar or Het; and Z^c is oxo, thio, sulfinyl, sulfonyl or imino of formula $-NR^{cb}-$ in which R^{cb} is (1-3C)alkyl or $R^{cc}R^{cd}N-(CH_2)_q-$ in

which q is the integer 2 or 3 and in which R^{cc} and R^{cd} are independently hydrogen or (1-3C)alkyl or the radical $R^{cc}R^{cd}N$ is pyrrolidino, piperidino or morpholino;

for a radical of formula Id, R^{da} is 1, 2 or 3;

for a radical of formula Ie, J^e is oxygen, sulfur or NR^{ea} in which R^{ea} is hydrogen or (1-3C)alkyl; R^{eb} is hydrogen, (1-6C)alkyl which may bear a hydroxy substituent and/or one to three fluoro substituents, (3-6C)alkenyl (in which a vinyl carbon is not bound to nitrogen), 2-hydroxyethyl, (3-7C)cyloalkyl, Ar or Het; R^{ec} is hydrogen, (1-6C)alkyl which may bear a hydroxy substituent and/or one to three fluoro substituents, (3-6C)cycloalkyl, (1-5C)alkoxy (only when J^e is oxygen), (3-6C)cycloalkoxy (only when J^e is oxygen), or an amino group of formula $NR^{ed}R^{ee}$ containing zero to seven carbon atoms in which each of R^{ed} and R^{ee} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{ed}R^{ee}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl group may bear a (1-3C)alkyl substituent at the 4-position);

for a radical of formula If, J^f is oxygen, sulfur or NR^{fa} in which R^{fa} is hydrogen or (1-3C)alkyl; L^f is a divalent hydrocarbon group in which the 1-position is bound to the carbon bearing the group J^f, the divalent group L^f being selected from trimethylene, cis-propenylene, tetramethylene, cis-butenylene, cis-but-3-enylene, cis,cis-butadienylene, pentamethylene and cis-pentenylene which divalent group L^f itself may bear one or two methyl substituents;

for a radical of formula Ig, Z^g is (1-8C)alkyl or (3-8C)cycloalkyl which may bear one or more substituents selected from the group consisting of halo, (3-6C)cycloalkyl, cyano, nitro, hydroxy, (1-4C)alkoxy, (1-5C)alkanoyloxy, aroyl, heteroaroyl, oxo, imino (which may bear a (1-6C)alkyl, (3-6C)cycloalkyl, (1-5C)alkanoyl or aroyl substituent), hydroxyimino (which hydroxyimino may bear a (1-4C)alkyl or a phenyl substituent on the oxygen), an amino group of formula $NR^{ga}R^{gb}$, an amino group of formula $NR^{gc}R^{gd}$, an amidino group of formula $C(=NR^{gg})NR^{ge}R^{gf}$, and a carbamoyl group of formula $CON(OR^{gh})R^{gi}$, but excluding any radical wherein a hydroxy and an oxo substituent together form a carboxy group, wherein an amino group of formula $NR^{ga}R^{gb}$ contains zero to seven carbon atoms and each of R^{ga} and R^{gb} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the

radical $NR^{ga}R^{gb}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent group at the 4-position); and wherein R^{gc} is hydrogen or (1-3C)alkyl and R^{gd} is (1-5C)alkanoyl, aroyl or heteroaroyl; or R^{gd} is a group of formula $C(=J^{g})NR^{ge}R^{gf}$ in which J^{g} is oxygen, sulfur, NR^{gg} or CHR^{gj}; and wherein the amino group $NR^{ge}R^{gf}$ contains zero to seven carbon atoms and each of R^{ge} and R^{gf} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{ge}R^{gf}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position) or R^{ge} is hydrogen or (1-4C)alkyl and R^{gf} together with R^{gg} forms an ethylene or trimethylene group; R^{gg} is hydrogen, (1-4C)alkyl or together with R^{gf} forms an ethylene or trimethylene group; R^{gj} is cyano, nitro or SO_2R^{gk} and R^{gk} is (1-4C)alkyl or phenyl; R^{gh} and R^{gi} are independently (1-3C)alkyl; and in which a cyclic group which is a substituent on Z^{g} or formed by substitution on Z^{g} may bear one or more (1-3C)alkyl groups on carbon as further substituents; and in which any aryl or heteroaryl group which is a part of the group Z^{g} may bear one or more halo, (1-4C)alkyl, (1-4C)alkoxy, cyano, trifluoromethyl or nitro substituents;

for a radical of formula Ih, G^{h} denotes a single bond, a double bond or a divalent hydrocarbon radical; J^{h} denotes a radical joined to the ring by a single bond if G^{h} denotes a double bond or, otherwise, a radical joined by a double bond; M^{h} denotes a heteroatom, a substituted heteroatom, or a single bond; and L^{h} denotes a hydrocarbon radical in which the 1-position is attached to M^{h}; wherein the values of G^{h}, J^{h}, M^{h} and L^{h} are selected from

(a) G^{h} is a single bond; J^{h} is oxo or thioxo; M^{h} is oxy, thio or NR^{ha}; and L^{h} is L^{ha};

(b) G^{h} is a single bond; J^{h} is NR^{hb}; M^{h} is NR^{ha}; and L^{h} is L^{ha};

(c) G^{h} is a double bond, J^{h} is OR^{ha}, SR^{ha} or $NR^{hc}R^{hd}$; M^{h} is nitrogen; and L^{h} is L^{ha};

(d) G^{h} is methylene which may bear one or two methyl substituents; J^{h} is oxo, thioxo or NR^{he}; M^{h} is oxy, thio, sulfinyl, sulfonyl or NR^{ha}; and L^{h} is L^{hb};

(e) G^h is a single bond; J^h is oxo, thioxo or NR^{he}; M^h is nitrogen; and L^h is L^{hc};

(f) G^h is methine, which may bear a (1-3C)alkyl substituent; J^h is oxo, thioxo or NR^{he}; M^h is nitrogen; and L^h is L^{hd};

(g) G^h is cis-vinylene, which may bear one or two methyl substituents; J^h is oxo, thioxo, or NR^{he}; M^h is nitrogen; and L^h is L^{he}; and

(h) G^h is a single bond; J^h is oxo or thioxo; M^h is a single bond; and L^h is L^{hf}; wherein

R^{ha} is hydrogen or (1-3C)alkyl; R^{hb} is hydrogen, (1-3C)alkyl, cyano, (1-3C)alkylsulfonyl or nitro; R^{hc} and R^{hd} are independently hydrogen or (1-3C)alkyl or the radical $NR^{hc}R^{hd}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{he} is hydrogen or (1-3C)alkyl; L^{ha} is ethylene, cis-vinylene, trimethylene or tetramethylene which radical L^{ha} itself may bear one or two methyl substituents; L^{hb} is ethylene or trimethylene which radical L^{hb} itself may bear one or two methyl substituents; L^{hc} is prop-2-en-1-yliden-3-yl, which radical L^{hc} itself may bear one or two methyl substituents; L^{hd} is cis-vinylene, which radical L^{hd} itself may bear one or two methyl substituents; L^{he} is methine, which radical L^{he} itself may bear a (1-3C)alkyl substituent; and L^{hf} is 4-oxabutan-1,4-diyl;

for a radical of formula Ij, X^j is (1-6C)alkyl, $-CH_2OR^{ja}$, $-CH_2SR^{ja}$, $-CH_2S(O)R^{jg}$, $-CH_2S(O)_2R^{jg}$, $-COR^{ja}$, $-COOR^{ja}$, $-C(=J^{ja})NR^{jb}R^{jc}$, $-C(R^{ja})(OR^{jd})(OR^{je})$, $-CH_2N(R^{ja})C(=J^{ja})R^{jf}$, $-CH_2N(R^{ja})COOR^{jg}$ or $-CH_2N(R^{ja})C(=J^{ja})NR^{jb}R^{jc}$;

B^j is a direct bond and L^j is a hydrocarbon chain in which the 1-position is bound to B^j and L^j is selected from trimethylene, tetramethylene, cis-1-butenylene and cis,cis-butadienylene; or B^j is $N(R^{jh})$ and L^j is a hydrocarbon chain selected from ethylene, trimethylene and cis-vinylene; or B^j is N and L^j is a hydrocarbon chain in which the 1-position is bound to B^j and L^j is cis,cis-prop-2-en-1-ylidin-3-yl; J^j and J^{ja} are independently oxygen or sulfur; R^{ja}, R^{jf} and R^{jh} are independently hydrogen or (1-6C)alkyl; R^{jb} and R^{jc} are

independently hydrogen or (1-6C)alkyl; or the radical $NR^{jb}R^{jc}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{jd} and R^{je} are independently (1-3C)alkyl or together form a divalent hydrocarbon chain selected from ethylene and trimethylene; R^{jg} is (1-6C)alkyl; and

for a radical of formula Ik, Z^k is a nitrogen linked radical of formula II wherein E^1, E^2, E^3 and E^4 form a divalent four membered chain ($-E^1=E^2-E^3=E^4-$) in which each of E^1, E^2, E^3 and E^4 is methine; or in which one or two of E^1, E^2, E^3 and E^4 is nitrogen and the remaining E^1, E^2, E^3 and E^4 are methine; and further wherein one or more of E^1, E^2, E^3 and E^4 which is methine may bear a halo, (1-3C)alkyl, hydroxy, (1-3C)alkoxy, (1-3C)alkylthio, (1-3C)alkylsulfinyl or (1-3C)alkylsulfonyl substituent; and wherein the radicals F^k, G^k, and $I^k(X^k)$ are selected from

(a) G^k is a direct bond, $I^k(X^k)$ is a radical having the formula $=C(Z^k)-$ and F^k is a radical selected from $-CH=$ and $-N=$;

(b) G^k is a direct bond, $I^k(X^k)$ is a radical having the formula $-C(=J^k)-$ and F^k is a radical selected from $-N(R^{kf})-$, $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-N(R^{kf})-$ and $-CH=N-$;

(c) G^k is a radical having the formula $-CH_2-$, $I^k(X^k)$ is a radical having formula $-C(=J^k)-$ and F^k is selected from $-CH_2-$ and $-N(R^{kf})-$; and

(d) G^k is selected from $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$ and $-N=CH-$, $I^k(X^k)$ is a radical having the formula $-C(=J^k)-$ and F^k is a direct bond; wherein

J^k is oxygen or sulfur; Z^k is $-OR^{ka}$, $-SR^{ka}$, $-COR^{ka}$, $-COOR^{ka}$, $-C(=J^{ka})NR^{kb}R^{kc}$ or $-C(R^{ka})(OR^{kd})(OR^{ke})$; J^{ka} is oxygen or sulfur; R^{ka} and R^{kf} are independently hydrogen or (1-6C)alkyl; R^{kb} and R^{kc} are independently hydrogen or (1-6C)alkyl; or the radical $NR^{kb}R^{kc}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{kd} and R^{ke} are independently (1-3C)alkyl or R^{kd} and R^{ke} together form ethylene or trimethylene; or Z^k is an imido radical selected from phthalimido, succinimido, maleimido, glutarimido, and 3-oxa-,

3-thia- and 3-azaglutarimido, in which the imido radical may bear one or more (1-3C)alkyl substituents and, in addition, the aromatic portion of the phthalimido may bear one or more halo, hydroxy or (1-3C)alkoxy substituents: and wherein

for a radical Q^1, Ar is a phenyl radical or an ortho-fused bicyclic carbocyclic radical of nine of ten ring atoms in which at least one ring is aromatic, which radical Ar may be unsubstituted or may bear one or more substituents selected from halo, cyano, trifluoromethyl, (1-4C)alkyl, (1-4C)alkoxy, methylenedioxy, hydroxy, mercapto, $-S(O)_nR^{xa}$, (1-5C)alkanoyl, (1-5C)alkanoyloxy, nitro, $NR^{xb}R^{xc}$, $NR^{xd}R^{xe}$, $C(=NR^{xf})NR^{xg}R^{xh}$, $CONR^{xb}R^{xc}$ and $COOR^{xj}$ wherein n is the integer 0, 1, or 2; R^{xa} is (1-6C)alkyl, (3-6C)cycloalkyl or phenyl (which phenyl may bear a halo, trifluoromethyl, (1-3C)alkyl or (1-3C)alkoxy substitutent); the radical $NR^{xb}R^{xc}$ contains zero to seven carbons and each of R^{xb} and R^{xc} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{xb}R^{xc}$ is pyrrolidino, piperidino, morpholino, thiomorpholine (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); and wherein R^{xd} is hydrogen or (1-4C)alkyl and R^{xe} is (1-5C)alkanoyl, benzoyl; or a group of formula $C(=J^x)NR^{xg}R^{xh}$ in which J^x is oxygen, sulfur, NR^{xf} or CHR^{xi}; R^{xf} is hydrogen, (1-5C)alkyl or together with R^{xg} forms an ethylene or trimethylene diradical, the radical $NR^{xg}R^{xh}$ contains zero to 7 carbons and each of R^{xg} amd R^{xh} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{xg}R^{xh}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); or R^{xg} together with R^{xf} forms an ethylene or trimethylene diradical and R^{xh} is hydrogen or (1-5C)alkyl; R^{xi} is cyano, nitro, (1-5C)alkylsulfonyl or phenylsulfonyl; and R^{xj} is hydrogen, (1-5C)alkyl or benzyl; and Het is a radical (or stable N-oxide thereof) attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms selected from oxygen, sulfur and nitrogen, or an ortho-fused bicyclic heterocycle derived therefrom by fusing a propenylene, trimethylene, tetramethylene or benz-diradical, which radical Het may be unsubstituted or may be substituted on carbon by one or more of the substituents defined above for Ar and may be substituted on nitrogen by (1-3C)alkyl;

Q^2 is phenyl which may bear one or two substituents independently selected from halo. trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl and methylenedioxy; or Q^2 is thienyl. imidazolyl, benzo[b]thiophenyl or naphthyl any of which may bear a halo substituent; or Q^2 is biphenylyl; or Q^2 is carbon-linked indolyl which may bear a benzyl substituent at the 1-position;

Q^3 is hydrogen, or (1-4C)alkyl; and

Q^4 is $-OR^2$ or $-NR^3R^4$; wherein

R^2 is hydrogen, (1-6C)alkyl, (3-7C)cycloalkyl, aryl(1-3C)alkyl or heteroaryl(1-3C)alkyl, wherein an aryl or heteroaryl group may bear one, two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-S(=O)_2NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, and methylenedioxy, and further wherein any arylethyl, arylpropyl, heteroarylethyl or heteroarylpropyl group may optionally be substituted at the position a to the aryl or heteroaryl group by a group selected from oxo, and $=NOR^{11}$;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl, (3-7C)cycloalkyl, aryl, heteroaryl, aryl(1-3C)alkyl and heteroaryl(1-3C)alkyl, wherein any aryl or heteroaryl group may bear one two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-S(=O)_2NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, and methylenedioxy, and further wherein any arylethyl, arylpropyl, heteroarylethyl or heteroarylpropyl group may optionally be substituted at the position a to the aryl or heteroaryl group by a group selected from oxo, and $=NOR^{11}$; or

$-NR^3R^4$ taken together represents a cyclic amino radical selected from pyrrolidinyl, piperidino, 1,2,3,6-tetrahydropyridyl, 1,2,3,4-tetrahydroquinolyl, and 1,2,3,4-tetrahydroisoquinolyl, which cyclic amino radical may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-S(=O)^2NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, phenyl, acetamidomethyl, and methylenedioxy; and

R^5-R^{11} are independently selected from hydrogen and (1-3C)alkyl

or the N-oxide of the nitrogen in Q^1 indicated by Δ in formulae Ia-Ik (or of either basic piperazinyl nitrogen of Q^1 when Z^a is nitrogen);

or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the nitrogen in Q^1 indicated by Δ in formulae Ia-Ik (or either basic piperazinyl nitrogen of Q^1 when Z^a is nitrogen) is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R^1 is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

Another particular sub-set of compounds of the invention are compounds of formula I wherein:

Q^1 is 4-hydroxy-4-phenylpiperidino. 4-acetamido-4-phenylpiperidino, 4-(2-methylsulfinylphenyl)piperidino. 4-(2-oxopiperidino)piperidino, or 4-(2-oxoperhydropyrimidin-1-yl)piperidino;

Q^2 is phenyl which may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl and methylenedioxy; or Q^2 is thienyl, imidazolyl, benzo[b]thiophenyl or naphthyl any of which may bear a halo substituent; or Q^2 is biphenylyl; or Q^2 is carbon-linked indolyl which may bear a benzyl substituent at the 1-position;

Q^3 is hydrogen; and

Q^4 is $-OR^2$ or $-NR^3R^4$; wherein

R^2 is hydrogen, (1-6C)alkyl, (3-7C)cycloalkyl, aryl(1-3C)alkyl or heteroaryl(1-3C)alkyl, wherein an aryl or heteroaryl group may bear one, two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-S(=O)_2NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, and methylenedioxy;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl, (3-7C)cycloalkyl, aryl, heteroaryl, aryl(1-3C)alkyl and heteroaryl(1-3C)alkyl, wherein any aryl or heteroaryl group may bear one two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-S(=O)_2NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, and methylenedioxy; or

the group $-NR^3R^4$ taken together represents a cyclic amino radical selected from pyrrolidinyl, piperidino, 1,2,3,6-tetrahydro-pyridyl, 1,2,3,4-tetrahydroquinolyl, and 1,2,3,4-tetrahydroiso-quinolyl, which cyclic amino radical may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-S(=O)_2NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, phenyl, acetamidomethyl, and methylenedioxy; and

R^5-R^{11} are independently selected from hydrogen and (1-3C)alkyl;

or the N-oxide of the nitrogen in Q^1;

or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the nitrogen in Q^1 is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R^1 is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

It will be appreciated that a compound of formula I may contains one or more asymmetically substituted carbon atoms and that such a compound may be isolated in optically active, racemic and/or diastereomeric forms. A compound may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, diastereomeric, polymorphic or stereoisomeric form, or mixture thereof, which form possesses NK1 and NK2 antagonist properties, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form or by synthesis from optically-active starting materials) and how to determine the NK1 and NK2 antagonist properties by the standard tests known in the art and those described hereinafter. It may be preferred to use the compound of formula I in a form which is characterized as containing, for example, at least 95%, 98% or 99% enantiomeric excess of the form which is of the (S)-configuration at the center indicated by * in formula I.

In this specification R^a, R^b, R^1, R^2, et cetera stand for generic radicals and have no other significance. It is to be understood that the generic terms "(1-3C)alkyl" and "(1-6C)alkyl" include both straight and branched chain alkyl radicals but references to individual alkyl radicals such as "propyl" embrace only the straight chain ("normal") radical, branched chain isomers such as "isopropyl" being referred to specifically. A similar convention applies to other generic groups, for example, alkoxy, alkanoyl, et cetera. Halo is

fluoro, chloro, bromo or iodo. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Heteroaryl encompasses a radical of a monocyclic aromatic ring containing five ring atoms, consisting of carbon and one to four heteroatoms selected from oxygen, sulfur and nitrogen or containing six ring atoms consisting of carbon and one or two nitrogens, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propenylene, trimethylene of tetramethylene diradical thereto, as well as a stable N-oxide thereof.

Particular values listed below for radicals, substituents and ranges are for illustration only and they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

A particular value for Ar is phenyl which may be unsubstituted or may bear a chloro, methyl, methoxy, hydroxy or methylsulfinyl substituent. A particular value for Het is furyl, thienyl, 2-imidazolyl, 1,3,4-oxadiazol-2-yl, pyridyl or pyrimidinyl which ring may be unsubstituted or may bear a chloro, methyl, methoxy, hydroxy, methylsulfinyl, methoxycarbonyl or ethoxycarbonyl substituent. A particular value for aryl is phenyl. A particular value for heteroaryl is furyl, pyridyl, imidazolyl, indolyl or pyrimidinyl. A particular value for halo is chloro or bromo. A particular value for (1-3C)alkyl is methyl, ethyl, propyl or isopropyl; for (1-4C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl; for (1-5C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl or isopentyl; for (1-6C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl or isohexyl; and for (1-8C)alkyl is methyl, ethyl, propyl, isopropyl, isopentyl, 1-ethylpropyl, hexyl, isohexyl, 1-propylbutyl, or octyl. A particular value for (3-6C)cycloalkyl is cyclopropyl, cyclopentyl or cyclohexyl; for (3-7C)cycloalkyl is cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl; and for (3-8C)cycloalkyl is cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. A particular value for (3-6C)alkenyl is allyl, 2-butenyl or 3-methyl-2-butenyl. A particular value for (1-4C)alkanoyl is formyl, acetyl, propionyl, butyryl or isobutyryl; and for (1-5C)alkanoyl is formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl or pivaloyl.

A more particular value for Ar is phenyl which may be unsubstituted or may bear a methoxy, or hydroxy substituent. A more particular value for Het is pyridyl or pyrimidinyl which ring may be unsubstituted or may bear a methoxy, hydroxy or methylsulfinyl substituent. A more particular value for heteroaryl is pyridyl. A more particular value for halo is chloro. A more particular value for (1-3C)alkyl is methyl; for (1-4C)alkyl is methyl or ethyl; for (1-5C)alkyl is methyl, ethyl, propyl or isopropyl; for (1-6C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl; and for (1-8C)alkyl is methyl, ethyl, propyl, isopropyl, 1-ethylpropyl or 1-propylbutyl. A more particular value for (3-6C)cylcoalkyl is cyclopropyl or cyclopentyl; for (3-7C)cycloalkyl is cyclopropyl or cyclopentyl; and for (3-8C)cycloalkyl is cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl. A more particular value for (3-6C)alkenyl is allyl. A more particular value for (1-4C)alkanoyl is formyl or acetyl; and for (1-5C)alkanoyl is formyl, acetyl, propionyl, butyryl or isobutyryl.

A particular value for Q^1 is 4-hydroxy-4-phenylpiperidino, 4-acetamido-4-phenylpiperidino, 4-(2-methylsulfinylphenyl)piperidino, 4-(2-oxopiperidino)piperidino, or 4-(2-oxoperhydropyrimidin-1-yl)piperidino; for Q^2 3,4-dichlorophenyl, or 3,4-methylenedioxyphenyl; for Q^3 is hydrogen; and for Q^4 is benzylamino, 4-phenylpiperidino, 4-methoxybenzylamino, cyclohexylamino, 4-methylbenzylamino, (benzyl)(methyl)amino, (methyl)(phenyl)amino, phenylamino, benzyloxy, (2-methoxybenzyl)-(methyl)amino, [3,5-bis(trifluoromethyl)benzyl](methyl)amino, 2-methoxybenzylamino, ethoxy, (3,5-dichloro-2-methoxybenzyl)amino, N-[3,5-dichloro-2-methoxybenzyl]-N-methylamino, a radical of formula VII wherein E is oxy and m is 1; a radical of formula VII wherein E is oxy and m is 2; or 3,5-bis(trifluoromethyl)benzylamino.

A more particular value for Q^1 is 4-acetamido-4-phenyl-piperidino or 4-hydroxy-4-phenylpiperidino; for Q^2 is 3,4-dichlorophenyl; and for Q^4 is (2-methoxybenzyl)(methyl)amino.

A particular group of compounds of formula I are compounds wherein Q^1 is a radical of formulae Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ij , Ik Im, In, Ip, Iq, Ir, Iu, Iv, Iw, or Ix.

A particular group of compounds of formula I are compounds wherein Q^1 is a radical of formulae Ie. If, Ig, Ih, Ij or Ik..

A particular group of compounds of formula I are compounds of formula III wherein. Q^1 and Q^4 have any of the values defined above.

A particular group of compounds of formula I are compounds wherein Q^4 is $-OR^2$.

A particular group of compounds of formula I are compounds wherein Q^4 is NR^3R^4.

A more particular group of compounds of formula I are compounds of formula III wherein Q^1 is a radical of formulae Ie, If, Ig, Ih, Ij or Ik.

A more particular group of compounds of formula I are compounds of formula III wherein. Q^4 is $-OR^2$.

A more particular group of compounds of formula I are compounds of formula III wherein, Q^4 is NR^3R^4.

A more particular group of compounds of formula I are compounds wherein Q^1 is a radical of formulae Ic, Id, Ie, If, Ig, Ih, Ij , Ik Im, In, Ip, Iq, Ir, Iu, Iv, Iw, or Ix as defined above. or a radical of formula Ib wherein Z^b is a substituted imino group $R^{ba}N$ or $R^{ba}CH_2N$ in which R^{ba} is (3-7C)cycloakyl, Ar. Het. Ar(carbonyl). Het(carbonyl), CH_2 $NR^{be}R^{bf}$, $C(=O)NR^{be}R^{bf}$, $CH_2C(=O)NR^{be}R^{bf}$; or Z^b is a disubstituted methylene group $R^{bb}(CH_2)_p$-C-R^{bc} in which R^{bb} is Ar or Het; p is the integer 0 or 1; and R^{bc} is hydrogen, hydroxy, (1-4C)alkoxy, (1-4C)alkanoyloxy, $COOR^{bd}$ (wherein R^{bd} is hydrogen or (1-3C)alkyl), cyano, CH_2 $NR^{be}R^{bf}$, $C(=O)NR^{be}R^{bf}$, $NR^{be}R^{bf}$ or SR^{bg} in which R^{be} and R^{bf} are independently hydrogen, (1-4C)alkyl, (1-4C)hydroxyalkyl or (1-4C)alkanoyl, or the radical $NR^{be}R^{bf}$ is pyrrolidino, piperidino or morpholino; and R^{bg} is hydrogen or (1-4C)alkyl.

Pharmaceutically acceptable salts of a compound of formula I include those made with a strong inorganic or organic acid which affords a physiologically acceptable anion, such as, for example, hydrochloric, sulfuric, phosphoric, methanesulfonic, or para-toluenesulfonic acid.

A compound of formula I may be made by processes which include processes known in the chemical art for the production of structurally analogous heterocyclic compounds. Such processes and intermediates for the manufacture of a compound of formula I as defined above are provided as further features of the invention and are illustrated by the following procedures in which the meanings of generic radicals are as defined above unless otherwise indicated:

(a) Acylating an amine of formula $-NR^3R^4$, with an ester of formula IV, wherein R^{12} is a suitable alkyl radical such as for example (1-3C)alkyl. The acylation may conveniently be carried out in a suitable solvent, such as for example diethyl ether, benzene or toluene, at a suitable temperature such as for example a temperature in the range of -50 to 100 °C preferably in the range of 0 to 60 °C. The reaction may conveniently be carried out in the presence of a trialkyl aluminum compound such as trimethylaluminum. Suitable conditions for the acylation are described in Example 1.

(b) For an acid addition salt of a compound of formula I, treating a corresponding compound of formula I which is in the free-base form, with an acid. The salt may conveniently be formed in a suitable solvent, such as for example diethyl ether, benzene or toluene. Suitable conditions for the formation of an acid-addition salt of a compound of formula I can be found at Example 2.

(c) Alkylating an amine of formula Q^1-H with an aldehyde of formula V by reductive alkylation. The alkylation may conveniently be carried out under conventional reductive alkylation conditions, for example by the in situ acid-catalyzed formation of an imminium salt, followed by reduction with sodium cyanoborohydride in alcoholic solvent. The reaction may be carried out in a suitable solvent at a temperature in the range of -20 to 100 °C, preferably in the range of 0 to 50 °C. Suitable conditions for the alkylation I can be found at Example 9.

(d) Acylating an amine of formula $-NR^3R^4$, with an acid of formula IV wherein R^{12} is a hydrogen. The acylation may conveniently be carried out in a suitable solvent, such as for example N,N-dimethylformamide or tetrahydrofuran, at a suitable temperature such as for example a temperature in the range of -50 to 100 °C preferably in the

range of 0 to 60 °C in the presence of a conventional coupling reagent. Suitable conditions for the acylation are described in Example 10.

(e) Alkylating an amine of formula Q^1-H with an alkylating agent of formula VI in which Y is a conventional leaving group such as for example iodide, bromide. methanesulfonate, p-toluenesulfonate. or trifluoromethanesulfonate. The reaction may be carried out under standard conditions for example in a suitable solvent at a temperature in the range of -20 to 100 °C, preferably in the range of 0 to 50 °C.

(f) For an N-oxide of the nitrogen in Q^1 indicated by Δ in formulae Ia-Ix (or of either basic piperazinyl nitrogen of Q^1 when Z^a is nitrogen); oxidizing the nitrogen of a corresponding compound of formula I using a conventional procedure. such as, for example, using hydrogen peroxide in methanol, peracetic acid. 3-chloroperoxybenzoic acid in an inert solvent (such as dichloromethane) or dioxirane in acetone.

(g) For a quaternary ammonium salt of the nitrogen in Q^1 indicated by Δ in formulae Ia-Ix (or either basic piperazinyl nitrogen of Q^1 when Z^a is nitrogen). alkylating the nitrogen in a corresponding compound of formula I with an alkylating agent of formula R^1Y wherein Y is a leaving group.

(h) For a compound of formula I which bears a sulfinyl group, oxidizing the sulfur of a corresponding compound of formula I which bears a sulfide group using a conventional method.

(i) For a compound of formula I which bears a sulfonyl group. oxidizing a sulfide or sulfinyl group of a corresponding compound of formula I using a conventional method.

(j) For a compound of formula I which bears an aromatic hydroxy group, cleaving the ether of a corresponding compound of formula I which bears an aromatic alkoxy group using a conventional method.

It may be desired to optionally use a protecting group during all or portions of the above described processes; the protecting group then may be removed when the final compound is to be formed.

Whereafter, for any of the above procedures, when a pharmaceutically acceptable salt of a compound of formula I is required, it may be obtained by reacting the

compound of formula I with an acid affording a physiologically acceptable counterion or by any other conventional procedure.

It will also be appreciated that certain of the various optional substituents in the compounds of the invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes above. and as such are included in the process aspect of the invention. The reagents and reaction conditions for such procedures are well known in the chemical art.

If not commercially available, the necessary starting materials for the above procedures may be made by procedures which are selected from standard techniques of organic chemistry, techniques which are analogous to the synthesis of known. structurally similar compounds and techniques which are analogous to the above described procedures or the procedures described in the Examples. The starting materials and the procedures for their preparation are additional aspects of the invention.

Piperidines of formula Q^1-H can be pepared from readily available starting materials using known synthetic methods. For example, preparations of piperidines of formula Q^1-H are disclosed in European Patent Applications, Publication Numbers (EPA) 428434, EPA 474561, EPA 512901, EPA 512902, EPA 515240 and EPA 559538, as well as in WO 94/10146, EPA 0625509 and EPA 0630887, WO 95/05377, WO 95/12577, WO 95/15961, EPA 680962, and WO 95/16682.. As will be clear to one skilled in the art, a variety of sequences are available for preparation of the starting materials, and the sequences leading to the starting materials and products of the invention may be altered if appropriate considerations regarding the synthetic methods and radicals present are followed.

The utility of a compound of the invention or a pharmaceutically acceptable salt thereof (hereinafter, collectively referred to as a "Compound") may be demonstrated by standard tests and clinical studies, including those disclosed in the EPA publications noted above, and those described below.

SP Receptor Binding Assay (Test A)

The ability of a Compound of the invention to antagonize the binding of SP at the NK1 receptor may be demonstrated using an assay using the human NK1 receptor expressed in Mouse Erythroleukemia (MEL) cells. The human NK1 receptor was isolated and characterized as described in: B. Hopkins, et al. "Isolation and characterization of the human lung NK1 receptor cDNA" Biochem. Biophys. Res. Comm., 1991, 180, 1110-1117; and the NK1 receptor was expressed in Mouse Erythroleukemia (MEL) cells using a procedure similar to that described in Test B below.

Neurokinin A (NKA) Receptor Binding Assay (Test B)

The ability of a Compound of the invention to antagonize the binding of NKA at the NK2 receptor may be demonstrated using an assay using the human NK2 receptor expressed in Mouse Erythroleukemia (MEL) cells, as described in: Aharony, D., et al. "Isolation and Pharmacological Characterization of a Hampster Neurokinin A Receptor cDNA" Molecular Pharmacology, 1994, 45, 9-19. In an initial use of this assay, the IC_{50} measured for the standard compound L-659,877 was found to be 30 nM versus ^{3}H-NKA binding to MELM.

The selectivity of a Compound for binding at the NK1 and the NK2 receptors may be shown by determining its binding at other receptors using standard assays, for example, one using a tritiated derivative of NKB in a tissue preparation selective for NK3 receptors. In general, the Compounds of the invention demonstrated statistically significant binding activity in Test A and Test B. Compounds having at least 25% inhibition at 1 μm were subject to Ki determination. For example, the compound of Example 1 demonstrated a Ki of 30 nanomolar in Test A, and a Ki of 15 nanomolar in Test B.

Rabbit Pulmonary Artery: NK1 in vitro functional assay (Test C)

The ability of a Compound of the invention to antagonize the action of the agonist, Ac-[Arg^6, Sar^9, Met(O$_2$)^{11}]SP(6-11) (designated ASMSP) in a pulmonary tissue may be demonstrated using a functional assay which is carried out under conditions similar to those described in: Emonds-Alt, X., et al. "In vitro and in vivo biological activities of Sr

140333. a novel potent non-peptide tachykinin NK_1 receptor antagonist" Eur. J. Pharmacol., 1993, 250, 403-413; and which is carried out as follows.

Male New Zealand white rabbits are killed by lethal injection (Nembutal. 60 mg/kg into a cannulated ear vein). Heparin. 0.0025 ml/kg of a 1000 U/ml solution. is injected into the ear vein prior to nembutal in order to decrease blood coagulation. The left and right branches of the pulmonary artery are isolated from the rest of the lung tissue and cut in half to provide four ring segments from each animal. The segments. with intact endothelium, are suspended between stainless steel stirrups and placed in water-jacketed (37.0°C) tissue baths containing physiological salt solution of the following composition (mM): NaCl, 119.0; KCl 4.6: $CaCl_2$, 1.8; $MgCl_2$, 0.5; NaH_2PO_4, 1.0; $NaHCO_3$, 25.0; glucose 11.0; indomethacin 0.005 (to inhibit cyclooxygenase): and dl-propranolol. 0.001 (to inhibit b-adrenergic receptors); gassed continuously with 95% O_2-5% CO_2. Initial tension placed on each tissue is 2 grams, which is maintained throughout a 0.5 hour equilibration period. Changes in tension are measured on a Grass polygraph via Grass FT-03 force transducers.

Thiorphan, 1 X 10^{-6}M (to inhibit E.C.3.4.24.11), and a selective NK2 antagonist (to inhibit NK_2 receptors) such as for example, an antagonist described in WO 94/148,184, EPA 0625509, EPA 0630887, or the antgonist SR48968 (3 X 10^{-8}M), are added to the tissue baths along with the test compound or its vehicle 90 minutes before the NK_1 receptor agonist, Ac-[Arg^6. Sar^9, $Met(O_2)^{11}$]SP(6-11) (designated ASMSP). Phenylephrine, 3 X 10^{-6}M, is added in order to induce tone in the tissue. One hour after introducing phenylephrine, cumulative concentration response effects of ASMSP are obtained and papaverine, 1 X 10^{-3}M, is added at the end of each experiment to determine the maximum magnitude of relaxation (defined as 100%).

Potencies of the compounds are determined by calculating the apparent dissociation constants (K_B) for each concentration tested using the standard equation:

K_B = [antagonist]/(dose ratio - 1)

where dose ratio = antilog[(agonist-log molar EC_{50} without compound) -

(agonist-log molar EC_{50} with compound)]. The K_B values are converted to the negative logarithms and expressed as -log molar K_B (i.e. pK_B). The potency of the agonist is determined at 50% of its own maximum relaxation in each curve. The EC_{50} values are converted to negative logarithms and expressed as -log molar EC_{50}. Maximum relaxation responses to ASMSP are determined by expressing the maximum response to the agonist as a percentage of the relaxation caused by papaverine.

Guinea Pig Trachea Assay: NK2 in vitro functional assay (Test D)

The ability of a Compound of the invention to antagonize the action of the agonist. [b-Ala8]-Neurokinin A(4-10) (designated BANK), in a pulmonary tissue may be demonstrated using a functional assay in guinea pig trachea which is carried out under conditions similar to those described in: Ellis. J.L.. et al.. "Pharmacological examination of receptors mediating contractile responses to tachykinins in airways isolated from human. guinea pig and hamster" J. Pharmacol. Exp. Ther., 1993, 267, 95-101; and which is carried out as follows.

Male guinea pigs are killed by a sharp blow to the back of the head followed by exsanguination. The trachea are removed. trimmed of excess tissue (including removal of epithelium) and cut in spiral fashion. Each longitudinally cut tracheal segment is suspended as a strip in a water-jacketed (37.5°C) tissue bath containing a physiological salt solution of the following composition (mM): NaCl, 119; KCl 4.6; $CaCl_2$, 1.8; $MgCl_2$. 0.5; NaH_2PO_4, 1; $NaHCO_3$, 25; glucose, 11; and indomethacin, 0.005 (to inhibit cyclooxygenase); gassed continuously with 95% O2-%5 CO_2. Initial tension placed on each tissue is 5 g, which is maintained throughout a 0.5 hour equilibration period before addition of other drugs. Contractile responses are measured on a Grass polygraph via Grass FT-03 force transducers.

Tissues are challenged once with a single concentration of capsaicin (1 X 10^{-6}M) and washed extensively before addition of a selective NK1 antagonist, such as for example (±)-CP96345 (3 X 10^{-7}M) (to block NK1 receptors) and thiorphan, 1 X 10^{-6}M (to block E.C.3.4.24.11). Cumulative addition of the NK_2 agonist [β-Ala8]-Neurokinin A(4-10) (designated BANK) is begun 35 minutes after addition of thiorphan. Test compound is added 120 min before BANK.

Potencies of the compounds are evaluated by calculating apparent dissociation constants (K_B) for each concentration tested using the standard equation:

K_B = [antagonist]/(dose ratio-1)

where dose ratio = antilog[(agonist -log molar EC_{50} without compound) - (agonist -log molar EC_{50} with compound)]. The K_B values are converted to the negative logarithms and expressed as -log molar K_B (i.e. pK_B). The potency of BANK is determined at 50% of its own maximum response level in each curve. The EC_{50} values are converted to the negative logarithms and expressed as -log molar EC_{50}. Maximum contractile responses to BANK are determined by expressing the maximum response to BANK as a percentage of the initial contraction caused by capasacin.

In general, the Compounds of the invention which were tested demonstrated functional activity in Tests C and D, with a pKB of 5 or greater typically being measured in each test. For Example, the compound of Example 1 demonstrated a pKB of 5.41 in Test C, and a pKB of 6.10 in Test D.

Guinea Pig Labored Abdominal Breathing (Dyspnea) Assay: NK_1 and NK_2 in vivo functional assay (Test E)

The activity of a compound as an antagonist of NK_1 or NK_2 receptors also may be demonstrated in vivo in laboratory animals, for example by adapting a routine guinea pig aerosol test described for evaluation of leukotriene antagonists in: Snyder, et al. "Conscious guinea-pig aerosol model for evaluation of peptide leukotriene antagonists" J. Pharmacol. Meth., 1988, 19, 219, which is carried out as follows.

Using the clear plastic chamber described previously by Snyder et al. to secure guinea pigs for a head-only aerosol exposure to bronchoconstrictor agonists, agonist is administered by aerosol to six conscious guinea pigs simultaneously during each maneuver. The tachykinin NK_1-selective agonist ASMSP or the tachykinin NK_2-selective agonist, BANK, 3 X 10^{-5}M of either, is aerosolized from a Devilbiss Model 25 ultrasonic nebulizer into an air stream entering the chamber at a rate of 2 L/minute.

Guinea pigs (275 - 400 g) are fasted for approximately 16 hours prior to experimentation. Compounds to be evaluated for blockade of effects of ASMSP or BANK or their vehicle (10% PEG400 in saline) are given by p.o.. i.v. or aerosol routes of administration at various times before aerosol agonist challenge. All animals are pretreated with atropine (10 mg/kg, i.p., 45 minutes pretreatment) indomethacin (10 mg/kg, i.p. 30 minutes pretreatment), propranolol (5 mg/kg, i.p., 30 minutes pretreatment), and thiorphan (1 mg/ml aerosol for 5 minutes. 15 minutes pretreatment).

Aerosol challenge with the agonist produces an initial increase in respiratory rate followed by a decrease with early signs of minor involvement of the abdominal muscles. The respiratory rate decreases further and the breathing becomes more labored with greater involvement of the abdominal muscles as exposure continues. The distinctly recognizable end point is the point where the breathing pattern of the guinea pig is consistently slow. deep, and deliberate. showing marked involvement of the abdominal muscles. Time. in seconds, from the onset of aerosol challenge to this end point is determined for each animal by using a stopwatch. The animals generally collapsed after reaching the end point and did not recover from the agonist-induced respiratory distress. Antagonists result in an increase in the time to reach the end point. Animals receive the aerosol administration of agonist for a maximum time of 780 seconds.

Differences between drug-treated groups and corresponding vehicle-treated control groups are compared using Student's t-test for unpaired observations. Results are reported as % protection values, where % protection =

[(drug time - mean control time)/(maximal aerosol time - mean control time)] X 100

<u>Clinical Studies</u>

Clinical studies to demonstrate the efficacy of a Compound of the invention may be carried out using standard methods. For example, the ability of a Compound to prevent or treat the symptoms of asthma or asthma-like conditions may be demonstrated using a challenge of inhaled cold air or allergen and evaluation by standard pulmonary

measurements such as, for example, FEV_1 (forced expiratory volume in one second) and FVC (forced vital capacity), analyzed by standard methods of statistical analysis.

It will be appreciated that the implications of a Compound's activity in the above desribed Tests is not limited to asthma, but rather, that the Tests provide evidence of general antagonism of both SP and NKA

SP and NKA have been implicated in the pathology of numerous diseases including: rheumatoid arthritis, Alzheimer's disease, oedema, allergic rhinitis, inflamation pain, gastrointestinal-hypermotility, anxiety, emesis, Huntington's Disease, Psycoses, hypertension, migraine, bladder hypermotility and uticaria. Accordingly, one feature of the invention is the use of a compound of formula I or a pharmaceutically acceptable salt thereof in the treatment of a disease in a human or other mammal in need thereof in which SP or NKA is implicated and antagonism of its action is desired.

Asthma is characterized by both chronic inflammation and hyperresponsiveness of the airways. The NK1 receptor is known to mediate inflammation and mucus hypersecretion in airways; and the NK2 receptor is involved in the control of the tone of bronchial smooth muscle. Thus, agents capable of antagonizing the actions of SP and NKA, at the NK1 and NK2 receptors, respectively, are capable of reducing both the chronic inflammation and the airway hyperresponsiveness which are symptomatic of asthma. It has been suggested that an antagonist having mixed affinity for NK1 and NK2 could be therapeutically superior to a receptor selective antagonist. C.M. Maggi "Tachykinin Receptors and Airway Pathophysiology" EUR. Respir. J., 1993, 6, 735-742 at 739. Also, it has been suggested that a synergistic effect against bronchoconstriction may result from the simultaneous application of an NK1 antagonist and an NK2 antagonist. D.M. Foulon, et al. "NK1 and NK2 Receptors Mediated Tachykinin and Resiniferatoxin-induced Bronchospasm in Guinea Pigs" American Review of Respiratory Disease, 1993, 148, 915-921. Accordingly, another feature of the invention is the use of a compound of formula I or a pharmaceutically acceptable salt thereof in the treatment of asthma in a human or other mammal in need thereof. Because of the range of effects attributable to the actions of SP and NKA, compounds which are capable of blocking their actions may also be useful as tools for further

evaluating the biological actions of other neurotransmitters in the Tachykinin family. As a result, another feature of the invention is provided by the use of a compound of formula I or a salt thereof as a pharmacological standard for the development and standardization of new disease models or assays for use in developing new therapeutic agents for treating diseases in which SP or NKA are implicated or for assays for their diagnosis.

When used in the treatment of a disease, a compound of the invention is generally administered as an appropriate pharmaceutical composition which comprises a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore and a pharmaceutically acceptable diluent or carrier, the composition being adapted for the particular route of administration chosen. Such a composition is provided as a further feature of the invention. It may be obtained employing conventional procedures and excipients and binders, and it may be one of a variety of dosage forms. Such forms include, for example, tablets, capsules, solutions or suspensions for oral administration; suppositories for rectal administration; sterile solutions or suspensions for administration by intravenous or intramuscular infusion or injection; aerosols or nebulizer solutions or suspensions for administration by inhalation; or powders together with pharmaceutically acceptable solid diluents such as lactose for administration by insufflation.

For oral administration a tablet or capsule containing up to 250 mg (and typically 5 to 100 mg) of a compound of formula I may conveniently be used. For administration by inhalation, a compound of formula I will be administered to humans in a daily dose range of, for example, 5 to 100 mg, in a single dose or divided into two to four daily doses. Similarly, for intravenous or intramuscular injection or infusion a sterile solution or suspension containing up to 10% w/w (and typically 0.05 to 5% w/w) of a compound of formula I may conveniently be used.

The dose of a compound of formula I to be administered will necessarily be varied according to principles well known in the art taking account of the route of administration and the severity of the condition and the size and age of the patient under treatment. However, in general, the compound of formula I will be administered to a warm-blooded animal (such as man) so that a dose in the range of, for example, 0.01 to 25 mg/kg (and usually 0.1 to 5 mg/kg) is received. It will be understood that generally

equivalent amounts of a pharmaceutically acceptable salt of a compound of formula I may be used.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 °C;

(ii) organic solutions were dried over anhydrous magnesium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals; 4.5-30 mm Hg) with a bath temperature of up to 60 °C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) melting points are uncorrected and (dec) indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;

(vi) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra;

(vii) yields are given for illustration only and are not necessarily those which may be obtained by diligent process development; preparations were repeated if more material was required;

(viii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using deuterated chloroform ($CDCl_3$) as solvent; conventional abbreviations for signal shape are used; for AB spectra the directly observed shifts are reported; coupling constants (J) are given in Hz; Ar designates an aromatic proton when such an assignment is made;

(ix) chemical symbols have their usual meanings; SI units and symbols are used:

(x) reduced pressures are given as absolute pressures in pascals (Pa); elevated pressures are given as gauge pressures in bars:

(xi) solvent ratios are given in volume:volume (v/v) terms; and

(xii) Mass spectra (MS) were run using an automated system with atmospheric pressure chemical ionization (ApCI). Methanol mobile phase enters the probe were it is pneumatically converted into an aerosol and rapidly heated into the gas phase at the probe tip. Hot gas from the probe enters the heated volume of the source which contains the corona discharge pin typically maintained at 3 kV. Methanol molecules rapidly react with ions from the corona discharge to produce stable reagent ions. Analyte molecules introduced into the mobile phase react with the reagent ions at atmospheric pressure and typically become protonated (for positive ions) or deprotonated (for negative ions). Where indicated, the following alternative methods of ionization were used: a) desorption chemical ionization (CI) using methane reagent gas and a direct exposure probe; b) electron impact (EI) or c) fast atom bombardment (FAB). Generally, only spectra where parent masses are observed are reported.

EXAMPLES

Example 1. N-Benzyl-5-(4-hydroxy-4-phenylpiperidino)-3-(3,4-dichlorophenyl)-pentanamide.

To a solution of benzylamine (191 mg) in toluene (2 mL) cooled to 0 °C was added trimethylaluminum (0.66 mL of a 2.0 M solution in toluene). The mixture was allowed to warm to room temperature over two hours. To this stirred solution was added ethyl 5-(4-hydroxy-4-phenyl-piperidino)-3-(3,4-dichlorophenyl)pentanoate (300 mg) in toluene. The solution was warmed to 60 °C for two hours and then stirred at room temperature overnight. The solution was diluted with dichloromethane and added to a mixture of brine and dichloromethane. The organic layer was separated and washed with brine. The aqueous layers were extracted with dichloromethane. The combined organic layers were dried, filtered and evaporated to afford an oil. Chromatography, with chloroform:methanol:ammonium hydroxide (97:3:0.25) as the eluent gave an oil which

crystallized upon exposure to diethyl ether:hexane to give the title compound (57 mg); mp 64-67 °C; MS (CI): m/z=513(M+1); NMR (CDCl$_3$, CF$_3$COOD): 1.27 (1,m), 2.22 (3,m), 2.39 (2,m), 2.77 (3,m), 3.15 (2,m), 3.32 (2,m), 3.56 (2,m), 4.21 (1,d), 4.45 (1,d), 6.96 (3,m), 7.34 (10,m). Analysis for $C_{29}H_{32}N_2O_2Cl_2$: Calculated: C, 68.09; H, 6.30; N, 5.47; Found: C, 68.01; H, 6.53; N, 5.24.

The intermediate ethyl 5-(4-hydroxy-4-phenylpiperidino)-3-(3,4-dichlorophenyl)-pentanoate was prepared as follows.

a. Ethyl 4,4-bis(tert-butoxycarbonyl)-3-(3,4-dichlorophenyl)-butanonate. To a stirred solution of bis(tert-butyl) malonate (13.7 g) in tetrahydrofuran (100 mL) was added potassium tert-butoxide (53.1 mL of a 1M solution in tetrahydrofuran). This mixture was stirred for 20 minutes and to it was added ethyl (E)-3-(3,4-dichloro-phenyl)-2-propenoate (12.96 g as a solution in tetrahydrofuran (30 mL)). The solution was stirred at room temperature for 1.5 hours and then diluted sequentially with diethyl ether (30 mL) and brine (30 mL). The organic layer was separated, dried, filtered, and evaporated to afford the tri-ester (22 g) as an oil; NMR: 7.53 (m,2), 7.28 (d,1, J=8.34), 3.91 (q,2, J=5.17), 3.8 (m,1), 3.55 (m,1), 2.72 (m,2), 1.4 (broad s,9), 1.13 (s,9), 1.01 (t,3, J=6.9).

b. Ethyl 4-carboxy-3-(3,4-dichlorophenyl)butanoate. Neat ethyl 4,4-bis(tert-butoxycarbonyl)-3-(3,4-dichlorophenyl)butanonate (22 g) was slowly heated to 180 °C for 4 hours. The material was allowed to cool to room temperature to yield the acid (14.4 g); NMR: 7.56 (m,2), 7.29 (dd,1, J=1.84, 8.35), 3.9 (q,2, J=7.07), 3.39 (m,1), 2.6 (m,4), 1.08 (t,3, J=7.03).

c. Ethyl 3-(3,4-dichlorophenyl)-5-hydroxypentanoate. Borane-methyl sulfide (1.76 mL of a 2.0 M solution in tetrahydrofuran) was added to a solution of ethyl 4-carboxy-3-(3,4-dichlorophenyl)-butanoate (5.34 g) in tetrahydrofuran (100 mL) over 20 minutes. The mixture was warmed to 50 °C for 2 hours. The solution was cooled to room temperature and diluted sequentially with water (100 ml) and ethyl acetate (350 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were dried, filtered and evaporated to afford an oil.

Chromatography with hexane:acetone (70:30) as eluent gave the alcohol as an oil (4.70 g); NMR: 7.3 (m,2), 7.07 (dd,1, J=2.14, 8.25), 4.0 (q,2, J=7.18), 3.5 (m,2), 3.0 (m,1), 2.6 (m,2), 1.9 (m,2), 1.16 (t,3, J=8.74).

d. Ethyl 3-(3,4-dichlorophenyl)-5-oxopentanoate. Pyridinium chlorochromate (3.5 g) was added to a solution of ethyl 3-(3,4-dichlorophenyl)-5-hydroxypentanoate (4.65 g) in dichloromethane (75 mL), at 0 °C. The stirred solution was brought to reflux for 1.5 hours. Additional pyridium chlorochromate (0.3 g) was added to the mixture, and it was brought back to reflux for an addition 0.75 hours. The mixture was cooled and filtered through FLORISIL [FLORISIL was purchased from the Aldrich Chemical Company of Milwaukee, Wisconsin, catalogue number 34,399-4]. The resulting filtrates were evaporated to give the aldehyde (3.75 g) as an oil that was used without further purification: NMR: 9.6 (s,1), 7.3 (m,2), 7.0 (m,1), 4.0 (m,2), 3.7 (m,1), 2.6 (m,4), 1.18 (m,3).

e. Ethyl 5-(4-hydroxy-4-phenylpiperidino)-3-(3,4-dichloro-phenyl)pentanoate. 4-Hydroxy-4-phenylpiperidine (2.74 g) was added to a solution of ethyl 3-(3,4-dichlorophenyl)-5-oxopentanoate (3.74 g) in methanol (80 mL) and the mixture was cooled to 0 °C. Glacial acetic acid was added until the pH was 5.5. Sodium cyanoborohydride (total 0.97 g) was added at one hour intervals in three equal portions. The mixture was allowed to warm to room temperature overnight. The mixture was diluted sequentially with aqueous sodium hydroxide (1N, 100 mL) and dichloromethane (200 mL). The organic layer was separated and extracted with brine. The aqueous layers were extracted with dichloromethane (3 x 200 mL). The combined organic layers were dried, filtered and evaporated to give an oil. Chromatography with chloroform:methanol:ammonium hydroxide (97:3:0.25) as the eluent gave the ester (1.6 g) as an oil; NMR: 7.3 (m,8), 4.0 (q,2, J=7.22), 3.1 (m,1), 2.0 (m,14), 1.17 (m,3).

Ethyl 5-(4-hydroxy-4-phenylpiperidino)-3-(3,4-dichloro-phenyl)pentanoate, described in sub-part e. above, is also a compound of the invention.

Example 2. 1-[5-(4-hydroxy-4-phenylpiperidino)-3-(3,4-dichloro-phenyl)valeryl]-4-phenylpiperidine hydrochloride salt.

To a solution of 1-[5-(4-hydroxy-4-phenylpiperidino)-3-(3,4-dichlorophenyl)-valeryl]-4-phenylpiperidine (0.18 g) in diethyl ether (20 mL) was added a solution of hydrochloric acid in diethyl ether (0.15 mL, 2N HCl). The solvent was evaporated to afford a solid. The solid was triterated two times with diethyl ether (20 mL) and dried overnight under reduced pressure to give the title salt as an off white solid (141.52 mg); mp 135-142 °C; MS (CI): m/z=567(M+1); NMR: 1.47 (m,6), 2.31 (m,4), 3.04 (m,12), 4.03 (m,1), 4.61 (broad d,1), 7.32 (m,13). Analysis for $C_{33}H_{38}Cl_2N_2O_2$•HCl•0.5 H_2O: Calculated: C, 65.94; H, 6.37; N, 4.66; Found: C, 64.98; H, 6.46; N, 4.34.

The intermediate 1-[5-(4-hydroxy-4-phenylpiperidino)-3-(3,4-dichlorophenyl)-valeryl]-4-phenylpiperidine, which is also a compound of the invention, was prepared using a procedure similar to that described in Example 1, except replacing the benzyl amine used therein with 4-phenylpiperidine.

Examples 3-8

Using a procedure similar similar to that described in Example 2, except replacing the 1-[5-(4-hydroxy-4-phenylpiperidino)-3-(3,4-dichlorophenyl)valeryl]-4-phenylpiperidine used therein with the requsite compound, the hydrochloride salts of the following compounds of formula I wherein Q^1 is 4-hydroxy-4-phenylpiperidine, Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen and Q^4 has the indicated values were prepared.

Example 3. Q^4=4-Methoxybenzylamino; mp 104-110 °C; MS (CI): m/z=543(M+1); NMR (CD_3OD): 1.97 (m,2), 2.23 (m,4), 2.61 (m,2), 2.84 (m,1), 3.33 (m,6), 3.75 (s,3), 3.99 (m,1), 4.33 (m,1), 6.81 (m,4), 7.35 (m,8). Analysis for $C_{30}H_{34}N_2Cl_2O_3$•HCl: Calculated: C, 62.34; H, 6.10; N, 4.84; Found: C, 62.16; H, 6.17; N, 4.90.

Example 4. Q^4=Cyclohexylamino; mp 112-117 °C; MS (CI): m/z=505(M+1); NMR (CD_3OD): 1.19 (m,5), 1.68 (m,5), 1.97 (m,2), 2.45 (m,6), 2.91 (m,1), 3.30 (m,7), 7.4 (m,8). Analysis for $C_{20}H_{36}Cl_2N_2O_2$•HCl•0.4 H_2O: Calculated: C, 62.28; H, 6.90; N, 5.18; Found: C, 61.50; H, 6.76; N, 4.82.

Example 5. Q^4=(4-Methylbenzyl)amino: mp 115-120 °C; MS (CI): m/z=527(M+1); NMR (CD_3OD): 1.97 (m,2), 2.29 (m,7), 2.63 (m,2), 2.88 (m,1), 3.29 (m,6), 4.03 (m,1), 4.32 (m,1), 6.83 (d,2), 7.03 (d,2), 7.34 (m,8). Analysis for $C_{30}H_{34}N_2Cl_2O_2$•HCl: Calculated: C, 64.11; H, 6.27; N, 4.98; Found: C, 63.98; H, 6.36; N, 5.05.

Example 6. Q^4=(Benzyl)(methyl)amino; mp 74-81 °C; MS (CI): m/z=527(M+1); NMR (CD_3OD): 2.10 (m,6), 2.87 (m,6), 3.39 (m,6), 4.31-4.66 (m,2), 7.3 (m,13). Analysis for $C_{30}H_{34}Cl_2N_2O_2$•HCl•0.5 H_2O: Calculated: C, 64.11; H, 6.27; N, 4.98; Found: C, 63.02; H, 6.22; N, 4.86.

Example 7. Q^4=(Methyl)(phenyl)amino: mp 96-102 °C; MS (CI): m/z=513(M+1); NMR (CD_3OD): 2.0 (broad m,6), 2.48 (broad d,2), 3.14 (m,7), 3.38 (m,3), 7.03 (m,3), 7.37 (m,11). Analysis for $C_{29}H_{32}Cl_2N_2O_2$•HCl•0.5 H_2O: Calculated: C, 63.56; H, 6.07; N, 5.11; Found: C, 62.68; H, 6.02; N, 5.05.

Example 8. Q^4=Anilino; mp 113-120 °C; MS (CI): m/z=499(M+1); NMR: 1.98 (m,24), 2.29 (m,4), 2.77 (m,3), 3.32 (m,6), 7.37 (m,13). Analysis for $C_{28}H_{30}Cl_2N_2O_2$•HCl•0.4 H_2O: Calculated: C, 62.98; H, 5.85; N, 5.24; Found: C, 62.17; H, 5.82; N, 5.49.

The intermediate amides used in Examples 3-8 were prepared using a sequence similar to that described in Example 1 and the sub-parts thereof, except replacing the benzylamine used therein with the requsite amine.

Example 9. Benzyl 5-(4-acetamido-4-phenylpiperidino)-3-(3,4-dichlorophenyl)pentanoate.

Benzyl 3-(3,4-dichlorophenyl)-5-oxopentanoate (0.850 g) was added to a solution of 4-acetamido-4-phenylpiperidine (0.58 g) in methanol (20 mL) and stirred for 5 minutes. Sodium cyanoborohydride (0.157 g) was added and the mixture adjusted to pH 5 by the addition of 5 drops of glacial acetic acid. The mixture was stirred at room temperature for 1.5 hours, and was evaporated. The resulting material was diluted with ethyl acetate, washed (saturated sodium bicarbonate, brine), dried, and evaporated to afford an oil. Chromatography with dichloromethane:methanol:ammonium hydroxide (95:5:0.1) as the eluent gave the title compound as a foamy white solid (0.52 g); mp 62-64 °C; MS (CI):

m/z=555(M+1); NMR: 1.70 (m,1), 1.86 (m,1), 2.00 (s,3), 2.14 (m,6), 2.34 (m,2), 2.66 (m,4), 3.18 (m,1), 5.02 (s,2), 5.47 (s,1), 7.01 (m,1), 7.01-7.40 (m,12). Analysis for $C_{31}H_{34}Cl_2N_2O_3{\cdot}0.5\ H_2O$: Calculated: C, 66.19; H, 6.27; N, 4.98; Found: C, 66.35; H, 6.09; N, 4.78.

The intermediate benzyl 3-(3,4-dichlorophenyl)-5-oxopentanoate was prepared as follows.

a. Benzyl 3-(3,4-dichlorophenyl)-2-propenoate. 3-(3,4-dichlorophenyl)-2-propenoic acid (20.0 g) was suspended in thionyl chloride (60 mL) and heated at reflux for 2 hours. The mixture was evaporated and the residue dissolved in dichloromethane (100 mL). To this solution was added benzyl alcohol (10.9 g) at 0 °C. The mixture was stirred at room temperature for 2 hours, diluted with an additional 100 mL of dichloromethane and washed with 1M HCl (100 mL), 1M NaOH (150 mL) and brine (100 mL). The organic phase was dried and evaporated. Recrystallization from diethyl ether:hexanes gave the ester (20.9 g) as a white solid.

b. Benzyl 4,4-bis(tert-butoxycarbonyl)-3-(3,4-dichlorophenyl)-butanonate. bis(Tert-butyl) malonate (16.3 g) in tetrahydrofuran (100 mL) was added to a solution of potassium tert-butoxide (79 mL, 1M in tert-butanol) and tetrahydrofuran (100 mL) dropwise at 10 °C. The mixture was allowed to warm gradually to room temperature and stirred an additional 40 minutes. The reaction was cooled to 5 °C and a solution of benzyl 3-(3,4-dichlorophenyl)-2-propenoate (21.0 g) in tetrahydrofuran (75 mL) was added dropwise over 15 minutes. The mixture was allowed to warm and stir at room temperature for 3 hours. A solution of saturated aqueous potassium phosphate monobasic (60 mL) was added to the reaction. The mixture was stirred 10 minutes, and was transfered to a separatory funnel containing ethyl ether (500 mL) and saturated aqueous potassium phosphate monobasic (100 mL). The ether phase was separated and the aqueous phase extracted with ether. The ether extracts were combined, washed (saturated sodium bicarbonate, brine), dried, and evaporated to give the tri-ester as an off-white solid (36.9 g); NMR: 7.31-7.03 (m,8), 4.97 (s,2), 3.75 (m,1), 3.45 (d,1, J=10), 3.00-2.90 (m,1), 2.73-2.49 (m,1), 1.45 (s,9), 1.23 (s,9); TLC: Rf = 0.72 (1:1 diethyl ether:hexane).

c. Benzyl 4-carboxy-3-(3,4-dichlorophenyl)butanoate. Benzyl 4,4-bis(tert-butoxycarbonyl)-3-(3,4-dichlorophenyl)butanonate (36.05 g) was treated with trifluoroacetic acid (150 mL) at 0 °C. The resulting suspension was warmed to room temperature and treated with dichloromethane (25 mL) to aid dissolution. After 1 hour the mixture was evaporated to afford a reddish oil, which was heated at 120 °C for 3 hours and then heated under vacuum (120 °C, 67 Pa) for 3 hours. The oil solidified upon cooling to afford the acid as a tan solid (22.8 g); NMR: 7.40-7.00 (m,8), 5.02 (s,2), 3.60 (m,1), 2.81-2.59 (m,4); MS (CI): m/z=367 (M+1); TLC: Rf = 0.21 (10:90:0.1 methanol:dichloromethane:ammonium hydroxide).

d. Benzyl 3-(3,4-dichlorophenyl)-5-hydroxypentanoate. Benzyl 4-carboxy-3-(3,4-dichlorophenyl)butanoate (7.34 g) was dissolved in tetrahydrofuran (100 mL). Borane-tetrahydrofuran complex (21 mL x 1M in tetrahydrofuran) was added dropwise and the solution was stirred for 1 hour at 0 °C. The mixture was heated at reflux for 1.5 hours. Additional borane-tetrahydrofuran complex (5 mL x 1M in tetrahydrofuran) was added at room temperature, and the reaction was again allowed to reflux for 1 hour. Saturated sodium bicarbonate (10 mL) was added to the reaction at 0 °C. The mixture was diluted with diethyl ether, mL), washed (saturated sodium bicarbonate, brine), dried, and evaporated to afford the alcohol as a yellow oil (7.07 g); NMR: 7.38-7.00 (m,8), 5.02 (s,1), 3.58-3.25 (m,3), 2.75-2.58 (m,2), 1.98-1.74 (m,3); TLC: Rf = 0.15 (1:1 diethyl ether:hexane).

e. Benzyl 3-(3,4-dichlorophenyl)-5-oxopentanoate. Benzyl 3-(3,4-dichlorophenyl)-5-hydroxypentanoate (1.60 g) was added to a dichloromethane (50 mL) solution containing N-methylmorpholine-N-oxide (0.80 g) and 4 Angstrom molecular sieves. The mixture was stirred for 15 minutes and tetrapropylammonium perruthenate (0.09 g) was added. After 1.5 hours, the mixture was diluted with dichloromethane (100 mL) washed (10% aqueous sodium sulfite, hydrochloric acid (1M x 50 mL), saturated sodium bicarbonate, brine), dried, and evaporated. Chromatographed through a short FLORISIL plug [FLORISIL was purchased from the Aldrich Chemical Company of Milwaukee, Wisconsin,

catalogue number 34,399-4] eluting with diethyl ether gave the aldehyde as a colorless oil (0.85 g); NMR: 9.67 (s,1), 7.45-7.18 (m,7), 7.03 (m,1), 5.03 (s,2), 3.71 (m,1), 2.80-2.58 (m,4); TLC: Rf = 0.26 (1:1 ethyl ether:hexane).

Example 10. 5-(4-Acetamido-4-phenylpiperidino)-3-(3,4-dichloro-phenyl)-N-(2-methoxybenzyl)-N-methylpentanamide.

5-(4-Acetamido-4-phenylpiperidino)-3-(3,4-dichlorophenyl)pentanoic acid (0.60 g) and N-(2-methoxybenzyl)-N-(methyl)amine hydrochloride (0.225 g) were combined in dry N,N-dimethylformamide (13 mL) under nitrogen. Triethylamine (0.121 g) was added followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide (0.595 g). The mixture was stirred overnight. The mixture was diluted with ethyl acetate and partitioned with saturated sodium bicarbonate. The aqueous phase was extracted with ethyl acetate and the organic extracts were combined, washed (brine), dried, and evaporated to afford an oil. Chromatography with dichloromethane:methanol:ammonium hydroxide (95:5:0.1) as the eluent gave the title compound as a white solid (0.248 g); mp 96-98 °C; MS (CI): m/z=598(M+1); NMR: 1.90-2.34 (m,10), 2.00 (s,3), 2.61-2.73 (m,4), 2.88 (s,3), 3.31 (m,1), 3.78 and 3.82 (s,3, two signals due to rotational isomers), 4,42-4.66 (m,2), 5.46 (broad,1), 6.80-6.93 (m,3), 7.02-7.39 (m,9). Analysis for $C_{33}H_{39}N_3Cl_2O_3 \cdot 0.20\ H_2O$: Calculated: C, 66.04; H, 6.62; N, 7.00; Found: C, 66.14; H, 6.57; N, 6.98.

The intermediate 5-(4-acetamido-4-phenylpiperidino)-3-(3,4-dichlorophenyl)-pentanoic acid was prepared as follows.

a. 5-(4-Acetamido-4-phenylpiperidino)-3-(3,4-dichlorophenyl)pentanoic acid. Benzyl 5-(4-acetamido-4-phenylpiperidino)-3-(3,4-dichlorophenyl)pentanoate (0.100 g) was dissolved in ethanol (35 mL) containing 10% Pd on carbon (0.050 g). The mixture was hydrogenated (2.4 bar, 1 hour). The resulting mixture was filtered through diatomaceous earth with ethanol. Evaporation of the resulting solution gave the acid as a waxy yellow solid (0.070 g), which had an NMR similar to the material prepared in sub-part b. below.

The intermediate 5-(4-acetamido-4-phenylpiperidino)-3-(3,4-dichlorophenyl)-pentanoic acid can alternativly be prepared as follows.

b. 5-(4-Acetamido-4-phenylpiperidino)-3-(3,4-dichlorophenyl)pentanoic acid. To a solution of ethyl 5-(4-acetamido-4-phenyl-piperidino)-3-(3,4-dichlorophenyl)pentanoate (1.00 g) (prepared as described in Example 15) in tetrahydrofuran (10 mL), and methanol (10 mL) was added a solution of lithium hydroxide monohydrate (0.22 g) in water (10 mL). The mixture was stirred for 16 hours, was acidified by addition of 1M HCl, and evaporated to afford the acid as a white powder (1.3 g); NMR: 8.42 (s,1), 7.62-7.55 (m,2), 7.35-7.31 (m,5), 7.22 (m,1), 3.35 (m,1), 3.14-2.95 (m,4), 2.79-2.30 (m,6), 2.16 (m,2), 2.09 (s,3), 1.91 (m,2); MS (CI): m/z=463(M+1); TLC: Rf=0.51 (10:1:0.1 tetrahydrofuran: water:acetic acid).

The intermediate 5-(4-acetamido-4-phenylpiperidino)-3-(3,4-dichlorophenyl)-pentanoic acid is also a compound of the invention.

Examples 11-14

Using a procedure similar to that described in Example 10, except replacing the N-methyl-N-(2-methoxybenzyl)amine with the requsite amine, the following compounds of formula I wherein Q^1 is 4-acetamido-4-phenylpiperidino, Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen and Q^4 is as defined were prepared.

Example 11. Q^4=Benzylamino; mp 173-174 °C; MS (CI): m/z=554(M+1); NMR (perdeuteriodimethylsulfoxide): 1.91 (s,3), 2.10-2.27 (m,4), 2.55 (m,3), 2.77 (m,2), 2.98-3.18 (m,5), 3.40 (m,3), 3.99-4.06 (m,1), 4.29-4.36 (m,1), 7.18-7.44 (m,9), 7.56-7.61 (m,2), 8.12 (broad,1), 8.36 (broad t,1), 10.26 (broad,1). Analysis for $C_{31}H_{35}Cl_2N_3O_2 \cdot 1.00\ H_2O \cdot 1.00\ HCl$: Calculated: C, 61.33; H, 6.31; N, 6.92; Found: C, 61.12; H, 6.43; N, 7.19.

Example 12. Q^4=(Methyl)[3,5-bis(trifluoromethyl)benzyl]amino; mp 84-86 °C; MS (CI): m/z=704(M+1); NMR: 1.72 (m,1), 2.00 (s,3), 2.00-2.36 (m,9), 2.70 (m,4), 2.93 (s,3), 3.33 (m,1), 4.61 (m,2), 5.46 (s,1), 7.10 (m,1), 7.19-7.39 (m,7), 7.56 (m,2), 7.81 (m,1).

Analysis for $C_{34}H_{35}Cl_2F_6N_3O_2$: Calculated: C, 58.13; H, 5.02; N, 5.98; Found: C, 58.07; H, 5.16; N, 5.80.

Example 13. Q^4=(Methyl)(benzyl)amino; mp 88-90 °C; MS (CI): m/z=568(M+1); NMR: 1.76 (m), 1.95-2.35 (m,9), 2.00 (s,3), 2.62-2.74 (m,4), 2.86 (d,3), 3.34 (m,1), 4.35-4.66 (m,2), 5.45 (broad,1), 6.95-7.40 (m,13). Analysis for $C_{32}H_{37}Cl_2N_3O_2$•1.00 H_2O: Calculated: C, 65.75; H, 6.72; N, 7.19; Found: C, 65.59; H, 6.34; N, 7.39.

Example 14. Q^4=(2-Methoxybenzyl)amino; mp 102-104 °C; MS (CI): m/z=582(M+1); NMR: 1.69 (m,2), 1.90-2.35 (m,9), 2.00 (s,3), 2.48-2.75 (m,3), 3.18 (m,1), 3.78 (s,3), 4.30 (m,2), 5.48 (broad,1), 5.77 (broad,1), 6.80-7.05 (m,4), 7.19-7.39 (m,8). Analysis for $C_{32}H_{37}Cl_2N_3O_3$•0.30 H_2O: Calculated: C, 65.37; H, 6.44; N, 7.15; Found: C, 65.34; H, 6.36; N, 7.21.

Example 15. Ethyl 5-(4-acetamido-4-phenylpiperidino)-3-(3,4-dichlorophenyl)pentanoate.

Using a sequence similar to that described in Example 9 and the sub-parts thereof, except replacing benzylalcohol with ethanol in sub-part a., the title compound was prepared as a white solid; mp 91-100 °C; NMR ($CDCl_3$, CF_3COOD): 7.64-7.59 (m,2), 7.4-7.3 (m,5), 7.30-7.20 (m,1), 4.0 (q,2), 3.46 (t,2), 3.23-3.03 (m,4), 2.93-2.67 (m,4), 2.17-2.0 (m,5), 1.9 (s,3), 1.1 (t,3); MS (CI): m/z=493(M+1); TLC: R_f=0.27 (95:5, dichloromethane:methanol). Analysis for $C_{26}H_{32}Cl_2N_2O_3$•0.50 H_2O: Calculated: C, 62.39; H, 6.65; N, 5.60; Found: C, 62.74; H, 6.53; N, 5.53.

Example 16. 4-Acetamido-1-[3-(3,4-dichlorophenyl)-4-(1,2,3,4-tetrahydroisoquinol-2-ylcarbonyl)butyl]-4-phenylpiperidine.

5-(4-Acetamido-4-phenylpiperidino)-3-(3,4-dichlorophenyl)pentanoic acid (0.276 g) in dimethylformamide (5 mL) was added to 1,2,3,4-tetrahydroisoquinoline (0.075 g), in a 16x100 mm tube. The reaction tube was vortexed to give a solution. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.106 g) was added and the mixture was stirred overnight at room temperature. The solvent was removed by centrifugal evaporation and the residue was partitioned between ethyl acetate (3 mL) and saturated

aqueous sodium bicarbonate solution (4 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2x3 mL). The combined organic extracts were evaporated to give material which was purified by chromatography using a Bond elut silica column. to give the title compound; MS: m/z=578(M+1). Analysis for $C_{33}H_{37}Cl_2N_3O_2$•1.0 H_2O: Calculated: C, 66.44; H, 6.59; N, 7.04; Found: C. 66.43; H, 6.39; N, 6.80. The procedure may conveniently be carried out with the assistance of a robot.

Examples 17-54

Using a procedure similar to that described in Example 16. except replacing the 1,2,3.4-tetrahydroisoquinoline with the requsite amine, the following compounds of formula I wherein Q^1 is 4-acetamido-4-phenylpiperidino, Q^2 is 3.4-dichlorophenyl, Q^3 is hydrogen and Q^4 is as defined. were prepared. Reaction products were analysed by high performance liquid chromatography on a HYPERSIL ODS column (4.6 x 250 mm), using a flow rate of 1.5 mL/minute. and UV detection (280 nm), with a column temperature of 40 °C. The eluents were prepared as follows:

Solvent 1 = 0.1% trifluoroacetic acid in water
Solvent 2 = 0.1% trifluoroacetic acid in acetonitrile
Solvent 3 = 1 mM triethylamine in water
Solvent 4 = 1 mM triethylamine in acetonitrile

Solvent A. linear gradient : time 0 minutes. 5:95 (Solvent 4:Solvent 3); time 3.0 minutes, 5:95 (Solvent 4:Solvent 3); time 17.0 minutes, 95:5 (Solvent 4; Solvent 3); time 18 minutes, 5:95 (Solvent 4:Solvent 3).

Solvent B, linear gradient: time 0 minutes, 75:25 (Solvent 2:Solvent 1); time 17.0 minutes, 75:25 (Solvent 2; Solvent 1); time 18 minutes, 95:5 (Solvent 2:Solvent 1); time 20 minutes, 75:25 (Solvent 2:Solvent 1).

Example 17. Q^4=4-Carbamoyl-4-phenylpiperidino; MS: m/z=649(M+1); HPLC: Solvent A, rt=11.07.

Example 18. Q^4=3-Phenyl-1-propylamino; MS: m/z=580(M+1); HPLC: Solvent A, rt=11.70.

Example 19. Q^4=3-Chlorobenzylamino; MS: m/z=586(M+1); HPLC: Solvent B, rt=15.27.

Example 20. Q^4=2-Thienylmethylamino; MS: m/z=558(M+1); HPLC: Solvent B, rt=6.86.

Example 21. Q^4=4-(Aminosulfonyl)phenethylamino: MS: m/z=645(M+1); HPLC: Solvent B, rt=4.54.

Example 22. Q^4=4-Phenyl-1,2,3,6-tetrahydropyrid-1-yl; MS: m/z=604(M+1); HPLC: Solvent B, rt=21.66.

Example 23. Q^4=4-(Dimethylamino)benzylamino; MS: m/z=595(M+1); HPLC: Solvent B, rt=6.06.

Example 24. Q^4=3,5-Dimethoxyanilino; MS: m/z=598(M+1); HPLC: Solvent B, rt=13.98.

Example 25. Q^4=3-(Imidazol-1-yl)propylamino; MS: m/z=570(M+1); HPLC: Solvent B, rt=6.13.

Example 26. Q^4=α-(Hydroximino)phenethylamino; MS: m/z=595(M+1); HPLC: Solvent B, rt=8.96.

Example 27. Q^4=2-(Imidazol-4-yl)ethylamino; MS: m/z=556(M+1); HPLC: Solvent B, rt=6.18.

Example 28. Q^4=3-Hydroxy-3-phenylpyrrolidin-1-yl; MS: m/z=608(M+1); HPLC: Solvent B, rt=7.56.

Example 29. Q^4=N-(Fur-2-ylmethyl)-N-methylamino; MS: m/z=556(M+1); HPLC: Solvent B, rt=12.85.

Example 30. Q^4=Fur-2-ylmethylamino; MS: m/z=542(M+1); HPLC: Solvent B, rt=6.13.

Example 31. Q^4=2-(Indol-3-yl)ethylamino; MS: m/z=605(M+1); HPLC: Solvent B, rt=12.55.

Example 32. Q^4=2-(5-Fluoroindol-3-yl)ethylamino; MS: m/z=623(M+1); HPLC: Solvent B, rt=12.83.

Example 33. Q^4=3,4-(methylenedioxy)benzylamino; MS: m/z=596(M+1); HPLC: Solvent B, rt=10.71.

Example 34. Q^4=4-Hydroxy-4-phenylpiperidino; MS: m/z=622(M+1); HPLC: Solvent B, rt=10.22.

Example 35. Q^4=Indan-1-ylamino; MS: m/z=578(M+1); HPLC: Solvent B, rt=15.60.

Example 36. Q^4=4-Phenylpiperidino; MS: m/z=606(M+1); HPLC: Solvent B, rt=22.10.

Example 37. Q^4=4-Acetamidomethyl-4-phenylpiperidino; MS: m/z=677(M+1);

Example 38. Q^4=N-Methyl-N-(2-pyridylmethyl)amino; MS: m/z=567(M+1); HPLC: Solvent B, rt=7.05.

Example 39. Q^4=N-Methyl-N-(6-methylpyrid-2-ylmethyl)amino; MS: m/z=581(M+1); HPLC: Solvent B, rt=7.28.

Example 40. Q^4=2-(Pyrid-2-yl)ethylamino; MS: m/z=567(M+1); HPLC: Solvent B, rt=6.58.

Example 41. Q^4=N-Methyl-N-(3-pyridylmethyl)amino; MS: m/z=567(M+1); HPLC: Solvent B, rt=6.74.

Example 42. Q^4=4-Pyridylmethylamino; MS: m/z=553(M+1); HPLC: Solvent B, rt=5.64.

Example 43. Q^4=3,5-Dimethylanilino; MS: m/z=566(M+1); HPLC: Solvent B, rt=20.55.

Example 44. Q^4=3,4-Dichlorobenzylamino; MS: m/z=624(M+1); HPLC: Solvent B, rt=16.75.

Example 45. Q^4=3-Methoxybenzylamino; MS: m/z=582(M+1); HPLC: Solvent B, rt=12.18.

Example 46. Q^4=2-Methoxyphenethylamino; MS: m/z=596.598(M+1); HPLC: Solvent B, rt=14.36.

Example 47. Q^4=4-Chlorophenethylamino; MS: m/z=602(M+1); HPLC: Solvent B, rt=18.64.

Example 48. Q^4=N-(Methyl)phenethylamino; MS: m/z=580(M+1); HPLC: Solvent B, rt=20.44.

Example 49. Q^4=3,4,5-Trimethoxyanilino; MS: m/z=628(M+1); HPLC: Solvent B, rt=10.67.

Example 50. Q^4=2-(1-Methylpyrrol-2-yl)ethylamino; MS: m/z=569(M+1); HPLC: Solvent B, rt=10.71.

Example 51. Q^4=2,6-Dichlorobenzylamino; MS: m/z=624(M+1); HPLC: Solvent B, rt=16.55.

Example 52. Q^4=N-Methyl-N-(2-pyrid-2-ylethyl)amino; MS: m/z=581(M+1); HPLC: Solvent B, rt=6.64.

Example 53. Q^4=3,4,5-Trimethoxybenzylamino; MS: m/z=642(M+1); HPLC: Solvent B, rt=9.57.

Example 54. Q^4=4-Aminobenzylamino; MS: m/z=567(M+1); HPLC: Solvent B, rt=5.63.

Example 55. N-methyl-N-(2-methoxybenzyl)-3-(3,4-dichlorophenyl)-5-(4-(2-methylsulfinylphenyl)piperidino)pentanamide hydrochloride salt.

To a stirred solution of N-methyl-N-(2-methoxybenzyl)-3-(3,4-dichlorophenyl)-5-oxopentanamide (0.135 g) in tetrahydrofuran (2 mL) was added 4-(2-methylsulfinylphenyl)piperidine (0.120 g) followed by acetic acid (0.026 g) and methanol (1 mL). The solution was stirred 10 minutes, sodium cyanoborohydride (0.025 g) in methanol (10 mL) was added, and the solution was allowed to stir for 2 hours. The solvent was evaporated

and the residue dissolved in ethyl acetate (20 mL) and extracted sequentially with saturated sodium bicarbonate (10 mL) and brine (10 mL). The organic phase was dried. filtered and evaporated. The resulting oil was purified by chromatography, with dichloromethane:methanol (82:8) as the eluent, to give the free base, which was converted to it's hydrochloride salt by dissolving in dichloromethane (5 mL) and treating with hydrogen chloride (6M dioxane solution. 0.5 mL). Evaporation gave the title amine hydrochloride (0.154 g) as a white solid; MS: m/z=601(M+1). Analysis for: $C_{32}H_{38}Cl_2N_2O_3S{\cdot}2.0\ H_2O{\cdot}1.0\ HCl$: Calculated: C, 57.02; H, 6.43; N, 4.16; Found: C, 56.98; H, 6.39; N, 4.24.

The intermediate N-methyl-N-(2-methoxybenzyl)-3-(3,4-dichlorophenyl)-5-oxopentanamide was prepared as follows.

a. 4-Ethoxycarbonyl-N-methyl-N-(2-methoxybenzyl)-3-(3,4-dichlorophenyl)-butanamide. 3-(3,4-Dichlorophenyl)-1,5-pentanedioic acid monoethyl ester (6.30 g) was added to a solution of oxalyl chloride (7.60 g) in dichloromethane (75 mL) at -15 °C followed by dimethylformamide (0.10 mL). The reaction was stirred 30 minutes at -15 °C . and 2 hours at room temperature. The reaction was evaporated. The residue was dissolved in dichloromethane (50 mL), cooled to 0 °C and treated with N-methyl-N-(2-methoxybenzyl)amine hydrochloride (4.00 g) followed by triethylamine (4.36 g). The solution was allowed to gradually warm to room temperature and stir overnight. The solution was diluted with dichloromethane (100 mL) and extracted sequentially with 1M HCl (100 mL), saturated sodium bicarbonate (100 mL) and brine (100 mL). The organic phase was dried and evaporated. The resulting oil was purified by chromatography, with diethyl ether as the eluent, to give the amide (8.35 g) as an oil.

b. 5-Hydroxy-N-methyl-N-(2-methoxybenzyl)-3-(3,4-dichlorophenyl)pentanamide. The compound from sub-part (a) (2.1g) was dissolved in tetrahydrofuran (80 mL) and treated with lithium borohydride (0.110 g). The mixture was heated at reflux for 5 hours, and stirred for 2 days at room temperature. The mixture was diluted with ethyl ether (120 mL) and extracted sequentially with 1M HCl (50 mL), saturated sodium bicarbonate (50 mL) and brine (50 mL). The organic phase was dried, evaporated, and purified by chromatography, with ethyl acetate as the eluent, to give the alcohol as an oil.

c. N-Methyl-N-(2-methoxybenzyl)-3-(3,4-dichlorophenyl)-5-oxopentanamide. A solution of dimethylsulfoxide (0.510 g) in dichloromethane (2 mL) was added to a solution of oxalyl chloride (0.368g) in dichloromethane (11 mL) dropwise at -78 °C. The mixture was stirred for 5 minutes at -78 °C and the compound from sub-part (b) (1.04 g) in dichloromethane (5 mL) was added. Stirring was continued for 20 minutes as the temperature was allowed to gradually rise to -50 °C. The temperature was returned to -78 °C, then triethylamine (1.32 g) was added. The solution was allowed to warm to room temperature and stir for 15 minutes. The solution was diluted with brine (100 mL) and extracted three times with dichloromethane (75 mL). The combined dichloromethane extracts were extracted successively with 1M HCl (100 mL), saturated sodium bicarbonate (100 mL) and brine (100 mL). The organic phase was dried and evaporated to give the aldehyde (1.00g) as an oil. The aldehyde was used without further purification.

Examples 56-58

Using a procedure similar to that described in Example 55, except replacing the 4-(2-methylsulfinylphenyl)piperidine with the requsite piperidine, the following compounds of formula I wherein Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen , Q^4 is N-(2-methoxybenzyl)-N-methylamino. and Q^1 is as defined were prepared.

Example 56. Q^1=4-(2-Oxo-2.3-dihydrobenzimidazol-1-yl)piperidino: MS: m/z=595(M+1). Analysis for: $C_{32}H_{36}Cl_2N_4O_3$•0.50 H_2O: Calculated: C, 63.57; H, 6.17; N, 9.27; Found: C, 63.55; H, 5.98; N, 9.32.

Example 57. Q^1=a radical of formula VIII; MS: m/z=609(M+1). Analysis for: $C_{33}H_{38}Cl_2N_4O_3$•0.40 H_2O: Calculated: C, 64.26; H, 6.34; N, 9.08; Found: C, 64.32; H, 6.26; N, 9.33.

Ecample 58. Q^1=4-Piperidinopiperidino; MS: m/z=546(M+1). Analysis for: $C_{30}H_{41}Cl_2N_3O_2$•0.40 H_2O•2.0 HCl: Calculated: C, 57.50; H, 7.04; N, 6.71; Found: C,57.39; H, 6.78; N, 6.84.

Examples 59-65

Using a procedure similar to that described in Example 16, except replacing the 1,2,3,4-tetrahydroisoquinoline with the requsite amine, the following compounds of formula I wherein Q^1 is 4-acetamido-4-phenylpiperidino, Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen and Q^4 is as defined, were prepared.

Example 59. Q^4=N-(3,5-Dichlorobenzyl)-N-methylamino; MS: m/z=634(M+1).

Example 60. Q^4=4-(Ethoxycarbonyl)anilino; MS: m/z=610(M+1).

Example 61. Q^4=N-methyl-N-(3-methoxyphenethyl)amino; MS: m/z=610(M+1). Analysis for: $C_{34}H_{41}Cl_2N_3O_3$•1.0 HCL: Calculated: C, 60.58; H, 6.73; N, 6.23; Found: C, 60.40; H, 6.40; N, 6.63.

Example 62. Q^4=N-Indan-1-yl-N-methylamino; MS: m/z=592(M+1). Analysis for: $C_{34}H_{39}Cl_2N_3O_2$•0.65 H_2O: Calculated: C, 67.58; H, 6.72; N, 6.95; Found: C, 67.51; H, 6.63; N, 6.97.

Example 63. Q^4=N=Methyl-N-(2-methoxyphenethyl)-amino; MS: m/z=610(M+1). Analysis for: $C_{34}H_{41}Cl_2N_3O_3$•0.70 H_2O•1.0 HCl: Calculated: C, 61.90; H, 6.63; N, 6.37; Found: C, 61.84; H, 6.52; N, 6.41.

Example 64. Q^4=3-Hydroxy-3-phenylpiperidino; MS: m/z=622(M+1).

Example 65. Q^4=4-Phenylpiperidino; MS: m/z=621(M+1). Analysis for: $C_{36}H_{44}Cl_2N_3O_2$•1.30 H_2O•1.0 Iodide: Calculated: C, 56.01; H, 6.08; N, 5.44; Found: C, 55.89; H, 5.80; N, 5.35.

Examples 66-67

Using a procedure similar to that described in Example 55, except replacing the 4-(2-methylsulfinylphenyl)piperidine, with 4-[(S*)-2-methylsulfinylphenyl]piperidine (prepared as described in International Patent Application Publication Number WO 95/16682 at Example 68), the following diasteroemers of formula I wherein Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen , Q^4 is N-(2-methoxybenzyl)-N-methylamino, and Q^1 is as defined, were

prepared. The product of the reaction was separated by high performance liquid chromatography on a CHIRACEL OD column (17.5 cm x 20 mm), with hexane:ethanol as the mobile phase. at a flow rate of 9 mL/minute, with UV detection (220 nm). The first diasteromer to elute from the column is described in Example 66 and the second to elute is described in Example 67.

Example 66. Q^1= 4-[(S*)-2-methylsulfinylphenyl]piperidino; MS: m/z=601(M+1). Analysis for: $C_{32}H_{38}Cl_2N_2O_3S$•1.40 H_2O•1.0 mandelic acid: Calculated: C, 61.67; H, 6.31; N, 3.60; Found: C, 61.70; H, 6.06; N, 3.75.

Example 67. Q^1= 4-[(S*)-2-methylsulfinylphenyl]piperidino; MS: m/z=601(M+1). Analysis for: C $C_{32}H_{38}Cl_2N_2O_3S$•1.20 H_2O•1.0 mandelic acid: Calculated: C, 61.96; H, 6.29; N, 3.61; Found: C, 61.80; H, 6.02; N, 3.76.

Examples 68-161

Using a procedure similar to that described in Example 16, except replacing the 1,2,3,4-tetrahydroisoquinoline with the requsite amine, the following compounds of formula I wherein Q^1 is 4-acetamido-4-phenylpiperidino, Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen and Q^4 is as defined, were prepared.

Example 68. Q^4=a radical of formula VII wherein E is oxy and m is 1; MS: m/z=594(M+1). Analysis for: $C_{33}H_{37}Cl_2N_3O_3$•0.65 H_2O•1.0 HCl: Calculated: C, 61.67; H, 6.16; N, 6.54; Found: C, 61.53; H, 6.22; N, 6.54.

Example 69. Q^4=4-(2-Thioxopyrrolidin-1-yl)piperidino; MS: m/z=629(M+1).

Example 70. Q^4=Norbornan-2-ylamino; MS: m/z=556(M+1).

Example 71. Q^4=Cyclopentylamino; MS: m/z=6530(M+1).

Example 72. Q^4=Cyclohexylamino; MS: m/z=544(M+1).

Example 73. Q^4=1,2,3,4-Tetrahydronaphth-1-ylamino; MS: m/z=592(M+1).

Example 74. Q^4=N-[(S)-α-Hydroxy-(R)-β-methylphenethyl]-N-(methyl)amino; MS: m/z=610(M+1).

Example 75. Q^4=1-Pyrrolidinylamino; MS: m/z=531(M+1).

Example 76. Q^4=2-(1-Methylpyrrolidin-2-yl)ethylamino; MS: m/z=573(M+1).

Example 77. Q^4=(1-Naphthylmethyl)amino; MS: m/z=602(M+1).

Example 78. Q^4=N.N-dibenzylamino; MS: m/z=642(M+1).

Example 79. Q^4=Thiazol-2-ylamino; MS: m/z=545(M+1).

Example 80. Q^4=(Tetrahydrofuran-2-ylmethyl)amino; MS: m/z=546(M+1).

Example 81. Q^4=(2-Indol-3-yl-1-methylethyl)amino; MS: m/z=619(M+1).

Example 82. Q^4=a radical of formula VIII; MS: m/z=676`(M+1).

Example 83. Q^4=(2-Pyridylmethyl)amino; MS: m/z=553(M+1).

Example 84. Q^4=2-(3-Pyridyl)piperidino; MS: m/z=607(M+1).

Example 85. Q^4=N-(1-Benzylpiperidin-4-yl)amino; MS: m/z=635(M+1).

Example 86. Q^4=3-Trifluoromethylbenzylamino; MS: m/z=620(M+1).

Example 87. Q^4=3-Methylbenzylamino; MS: m/z=566(M+1).

Example 88. Q^4=α-(Phenyl)phenethylamino; MS: m/z=642(M+1).

Example 89. Q^4=(2-Ethylhexyl)amino; MS: m/z=574(M+1).

Example 90. Q^4=3-(Carbamoyl)piperidino; MS: m/z=573(M+1).

Example 91. Q^4=(3,3-Dimethylbutyl)amino; MS: m/z=546(M+1).

Example 92. Q^4=N-Benzyl-N-(ethoxycarbonylmethyl)amino; MS: m/z=638(M+1).

Example 93. Q^4=N-Butyl-N-methylamino; MS: m/z=532(M+1).

Example 94. Q^4=2-Indanylamino; MS: m/z=578(M+1).

Example 95. Q^4=N-Methyl-N-(1-naphthylmethyl)amino; MS: m/z=616(M+1).

<u>Example 96.</u> Q^4=6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinol-2-yl; MS: m/z=638(M+1).

<u>Example 97.</u> Q^4=α-Oxophenethylamino; MS: m/z=580(M+1).

<u>Example 98.</u> Q^4=N-Ethyl-N-(4-pyridylmethyl)amino; MS: m/z=581(M+1).

<u>Example 99.</u> Q^4=(cyclopropylmethyl)amino; MS: m/z=516(M+1).

<u>Example 100.</u> Q^4=4-Acetyl-4-phenylpiperidino; MS: m/z=648(M+1).

<u>Example 101.</u> Q^4=N-[(R)-α-methylbenzyl]-N-methylamino; MS: m/z=580(M+1).

<u>Example 102.</u> Q^4=(R)-N-(1-Naphth-1-ylethyl)amino; MS: m/z=616(M+1).

<u>Example 103.</u> Q^4=(S)-N-(1-Naphth-1-ylethyl)amino; MS: m/z=616(M+1).

<u>Example 104.</u> Q^4=N-[(R)-α-Hydroxy-(S)-β-methylphenethyl]-N-methylamino; MS: m/z=610(M+1).

<u>Example 105.</u> Q^4=(R)-α-methylbenzylamino; MS: m/z=566(M+1).

<u>Example 106.</u> Q^4=(S)-α-methylbenzylamino; MS: m/z=566(M+1).

<u>Example 107.</u> Q^4=4-(4-Bromophenyl)-4-hydroxypiperidino; MS: m/z=700(M+1).

<u>Example 108.</u> Q^4=N-Methyl-N-[(R)-α-methylbenzyl]amino; MS: m/z=580(M+1).

<u>Example 109.</u> Q^4=N-(3,4-Dimethoxyphenethyl)-N-methylamino; MS: m/z=640(M+1).

<u>Example 110.</u> Q^4=[(1S,2S)-4,4-Dimethyl-3,5-dioxacyclohex-1-yl]amino (a radical of formula IX); MS: m/z=652(M+1).

<u>Example 111.</u> Q^4=1-Adamantylamino; MS: m/z=596(M+1).

<u>Example 112.</u> Q^4=(3-Adamanthylmethyl)amino; MS: m/z=610(M+1).

<u>Example 113.</u> Q^4=Quinuclidin-3-ylamino; MS: m/z=571(M+1).

Example 114. Q^4=(Cyclohexylmethyl)amino: MS: m/z=558(M+1).

Example 115. Q^4=(S)-β-Methoxycarbonyl-4-hydroxyphenethylamino: MS: m/z=640(M+1).

Example 116. Q^4=4,5-Dihydrothiazol-2-ylamino; MS: m/z=547(M+1).

Example 117. Q^4=N-(2-Indol-3-ylethyl)-N-methylamino; MS: m/z=619(M+1).

Example 118. Q^4=2-(5-Methoxyindol-3-yl)ethylamino; MS: m/z=635(M+1).

Example 119. Q^4=2-(6-Methoxyindol-3-yl)ethylamino; MS: m/z=635(M+1).

Example 120. Q^4=Benzothiazo-2-ylamino: MS: m/z=595(M+1).

Example 121. Q^4=4-Phenylpiperazin-1-yl; MS: m/z=607(M+1).

Example 122. Q^4=4-Benzylpiperidino: MS: m/z=620(M+1).

Example 123. Q^4=2-Pyridylamino; MS: m/z=539(M+1).

Example 124. Q^4=(3-Pyridylmethyl)amino; MS: m/z=553(M+1).

Example 125. Q^4=2-Fluorobenzylamino; MS: m/z=570(M+1).

Example 126. Q^4=2,4-Dichlorobenzylamino: MS: m/z=621(M+1).

Example 127. Q^4=2-Ethozybenzylamino: MS: m/z=596(M+1).

Example 128. Q^4=3-Fluorobenzylamino; MS: m/z=570(M+1).

Example 129. Q^4=2-Adamantylamino; MS: m/z=596(M+1).

Example 130. Q^4=3,4-Dimethoxybenzylamino; MS: m/z=612(M+1).

Example 131. Q^4=4-Fluorobenzylamino; MS: m/z=570(M+1).

Example 132. Q^4=4-Methoxybenzylamino; MS: m/z=582(M+1).

Example 133. Q^4=4-Methylbenzylamino; MS: m/z=566(M+1).

Example 134. Q^4=(2-Methylbutyl)amino; MS: m/z=532(M+1).

Example 135. Q^4=Phenethylamino; MS: m/z=566(M+1).

Example 136. Q^4=2-Chlorophenethylamino; MS: m/z=601(M+1).

Example 137. Q^4=3-Methoxyphenethylamino; MS: m/z=596(M+1).

Example 138. Q^4=4-Bromophenethylamino; MS: m/z=644(M+1).

Example 139. Q^4=(3-Methylbutyl)amino; MS: m/z=532(M+1).

Example 140. Q^4=(4-Phenylbutyl)amino; MS: m/z=594(M+1).

Example 141. Q^4=(butyl)(ethyl)amino; MS: m/z=546(M+1).

Example 142. Q^4=2,6-Difluorobenzylamino; MS: m/z=588(M+1).

Example 143. Q^4=3,4,5,6-Tetrahydrophenethylamino; MS: m/z=570(M+1).

Example 144. Q^4=N-[(S)-β-(Ethoxycarbonyl)phenethyl]amino; MS: m/z=638(M+1).

Example 145. Q^4=9-Fluorenylamino; MS: m/z=626(M+1).

Example 146. Q^4=(α-Phenylbenzyl)amino; MS: m/z=628(M+1).

Example 147. Q^4=(5-Oxo-4,5-dihydropyrazol-3-yl)amino; MS: m/z=544(M+1).

Example 148. Q^4=4-Aminocarbonyl-4-(isopropylamino)piperidino; MS: m/z=630(M+1).

Example 149. Q^4=4-(Morpholinocarbonyl)-4-phenylpiperidino; MS: m/z=719(M+1).

Example 150. Q^4=4-Piperidinocarbonyl-4-phenylpiperidino; MS: m/z=717(M+1).

Example 151. Q^4=3,5-Dichlorobenzylamino; MS: m/z=620(M+1).

Example 152. Q^4=1-Phenyl-4,5-dihydropyrazol-3-ylamino; MS: m/z=606(M+1).

Example 153. Q^4=(1-Benzylpyrrolidin-3-yl)amino; MS: m/z=621(M+1).

Example 154. Q^4=N-Benzyl-N-[(S)-α-methylbenzyl]amino; MS: m/z=656(M+1).

Example 155. Q^4=4-Aminocarbonyl-4-(methylamino)piperidino; MS: m/z=602(M+1).

Example 156. Q^4=;3-Methyl-3-phenylpiperidino MS: m/z=620(M+1).

Example 157. Q^4=(5-Methylfuran-2-ylmethyl)amino; MS: m/z=556(M+1).

Example 158. Q^4=4-(2-Oxobenzimidazolidin-1-yl)piperidino: MS: m/z=662(M+1).

Example 159. Q^4=4-(Aminocarbonyl)-4-(4-piperidyl)piperidino: MS: m/z=656(M+1).

Example 160. Q^4=(5-Methyl-1.3.4-thiadiazol-2-yl)amino; MS: m/z=560(M+1).

Example 161. Q^4=a radical of formula X; MS: m/z=696(M+1).

Examples 162-163

Using a procedure similar to that described in Example 16. except replacing the 1,2,3,4-tetrahydroisoquinoline with the requsite amine. the following compounds of formula I wherein Q^1 is 4-acetamido-4-phenylpiperidino, Q^2 is 3.4-dichlorophenyl, Q^3 is hydrogen and Q^4 is as defined. were prepared..

Example 162. Q^4=N-Ethyl-N-(2-methoxybenzyl)amino; MS (CI): m/z=610(M+1). Analysis for $C_{34}H_{41}Cl_2N_3O_3$•1.0 HCl•0.5H_2O: Calculated: C, 62.24; H, 6.60; N, 6.40; Found: C, 62.15; H, 6.55; N, 6.45.

Example 163. Q^4=N-(3,5-Dimethylbenzyl)-N-methylamino; MS (CI): m/z=594(M+1). Analysis for $C_{34}H_{41}Cl_2N_3O_2$•1.0 HCl•1.6 H_2O: Calculated: C, 61.88; H, 6.90; N, 6.37; Found: C, 61.77; H, 6.64; N, 6.10.

Example 164. 5-(4-Acetamido-4-phenylpiperidino)-3-(3.4-dichlorophenyl)-N-[3,5-bis(trifluoromethyl)benzyl]pentanamide.

Using a procedure similar to that described in Example 1, except replacing ethyl 5-(4-hydroxy-4-phenylpiperidino)-3-(3,4-dichlorophenyl)pentanoate with ethyl 5-(4-acetamido-4-phenyl-piperidino)-3-(3,4-dichlorophenyl)pentanoate and replacing benzyl amine with bis(trifluoromethyl)benzylamine. the title compound was prepared; mp 130-138 °C; MS: m/z=690(M+1); NMR (dimethylsulfoxide-d6): 1.93 (s,3), 2.0-2.18 (m,4), 2.50-2.70 (m,4). 2.79-2.94 (broad,1), 3.0-3.26 (m,4), 3.50 (t,2), 4.23-4.53 (m,2), 7.10-7.63 (m,8). 7.80 (s,2). 7.89 (s,1). Analysis for $C_{33}H_{33}Cl_2F_6N_3O_2$: Calculated: C, 57.57; H, 4.83; N, 6.10: Found: C, 57.62: H. 5.03; N, 5.94.

Examples 165-170

Using a procedure similar to that described in Example 16, except replacing the 1,2,3,4-tetrahydroisoquinoline with the requsite amine. the following compounds of formula I wherein Q^1 is 4-acetamido-4-phenylpiperidino, Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen and Q^4 is as defined. were prepared..

Example 165. Q^4=N-(3,5-Dimethylbenzyl)amino; MS: m/z=580(M+1). Analysis for $C_{33}H_{39}Cl_2N_3O_2 \cdot 0.35\ H_2O$: Calculated: C, 67.49; H, 6.82; N, 7.73; Found: C, 67.48: H. 6.71; N. 7.06.

Example 166. Q^4=Anilino; MS: m/z=538(M+1). Analysis for $C_{30}H_{33}Cl_2N_3O_2 \cdot 0.30\ H_2O$; Calculated: C, 66.24; H. 6.23; N, 7.73; Found: C, 66.44; H, 6.17; N, 7.51.

Example 167. Q^4=N-Methyl-N-(phenylsulfonyl)amino; MS: m/z=616(M+1).

Example 168. Q^4=Phenylsulfonylamino; MS: m/z=602(M+1).

Example 169. Q^4=N-Methoxy-N-methylamino; MS: m/z=506(M+1).

Example 170. Q^4=3,5-Dichloroanilino; MS: m/z=606(M+1). Analysis for $C_{30}H_{31}Cl_4N_3O_2 \cdot 0.23\ H_2O$: Calculate: C, 58.92; H, 5.18; N, 6.87; Found: C, 58.91; H, 5.20; N, 6.94.

Example 171. (R*)-5-(4-Acetamido-4-phenylpiperidino)-3-(3,4-dichlorophenyl)-N-(2-methoxybenzyl)-N-methylpentanamide.

Using a procedure similar to that described in Example 16, except replacing the 1,2,3,4-tetrahydroisoquinoline with 4-acetamido-4-phenylpiperidine, and replacing the racemic 5-(4-acetamido-4-phenylpiperidino)-3-(3,4-dichlorophenyl)pentanoic acid with the requsite enantiomer, the title compound was prepared: MS: m/z=596(M+1). Analysis for $C_{33}H_{39}Cl_2N_3O_3$•0.30 H_2O: Calculated: C, 65.84; H, 6.63; N, 6.98; Found: C, 65.74; H, 6.58; N, 7.10.

Example 172. (S*)-5-(4-Acetamido-4-phenylpiperidino)-3-(3,4-dichlorophenyl)-N-(2-methoxybenzyl)-N-methylpentanamide

Using a procedure similar to that described in Example 16, except replacing the 1,2,3,4-tetrahydroisoquinoline with 4-acetamido-4-phenylpiperidine, and replacing the racemic 5-(4-acetamido-4-phenylpiperidino)-3-(3,4-dichlorophenyl)pentanoic acid with the requsite enantiomer, the title compound was prepared: MS: m/z=596(M+1). Analysis for $C_{33}H_{39}Cl_2N_3O_3$•0.2 H_2O: Calculated: C, 66.04; H, 6.62; N, 7.00; found: C, 66.04; H, 6.67; N, 7.16.

The intermediate chiral acids used for the preparation of the compounds of Examples 169 and 170 were prepared as follows. These acids are also compounds of the invention.

A racemic mixture of the ethyl ester of Example 15 was resolved by high performance liquid chromatogyaphy using a Chiracel OD (50mm x 50 cm) column, with hexane:ethanol (50:50) as the eluent and a flow rate of 54 mL/minute. The first ester enantiomer to elute had a retention time of 14 minutes. This ester was hydrolysed under standard conditions to give the corresponding acid. The acid was used for the coupling reaction in Example 169. The second ester enantiomer to elute had a retention time of 19 minutes. This ester was hydrolysed under standard conditions to give the corresponding acid. The acid was used for the coupling reaction in Example 170.

Example 173. 5-[4-(2-Oxoperhydropyrimidin-1-yl)piperidino]-3-(3,4-dichlorophenyl)-N-(2-methoxybenzyl)-N-methylpentanamide.

3-(3,4-Dichlorophenyl)-N-(2-methoxybenzyl)-N-methyl-5-oxopentanamide (0.1 molar in tetrahydrofuran, 5 mL) was added through a syringe to 2-oxoperhydropyrimidin-1-

ylpiperidine (0.5 mmol) and the mixture was pulse-vortexed for 30 seconds. Glacial acetic acid (0.7 mmol) was added and the solution was allowed to stir for 10 minutes at room temperature. A solution of sodium cyanoborohydride in methanol (0.08 molar. 10 mL) was added in 4 portions with pulse-vortexing between each addition. The reaction was allowed to stir over night and the volume was decreased to approximately 3 mL using a centrifugal evaporator. Ethyl acetate was added and the soulution was pulse-vortexed for for 30 seconds. The solution was taken up using a canula and transfered to a 25x150 mm tube. Ethyl acetate (2 mL) and saturated aqueous sodium bicarbonate (9 mL) were added and the mixture was pulse-vortexed. After 20 minutes, the aqueous layer was removed and the organic layer was washed with brine (8 mL). After 20 minutes. the brine was removed and the organig solution was concentrated using a centrifugal evaporator. The concentrate was transfered to vials and evaporated to give the title compound: MS: m/z=561(M+1). Analysis for $C_{29}H_{38}Cl_2N_4O_3{\bullet}0.50\ H_20$: Calculated: C, 61.05; H, 6.89; N, 9.82; Found: C, 61.04; H. 6.73; N. 9.73. The procedure may conveniently be carried out with the assistance of a robot.

Examples 174-177

Using a procedure similar to that described in Example 173, except replacing the 2-oxoperhydropyrimidin-1-ylpiperidine with the requsite piperidine. the following compounds of formula I wherein Q^2 is 3.4-dichlorophenyl, Q^3 is hydrogen , Q^4 is N-(2-methoxybenzyl)-N-methylamino, and Q^1 is as defined were prepared.

Example 174. Q^1=4-(2-Oxopiperidino)piperidino; MS: m/z=560(M+1). Analysis for $C_{30}H_{30}Cl_2N_3O_3{\bullet}0.55\ H_2O$: Calculated: C, 63.16; H, 7.08; N, 7.37; Found: C, 63.14; H, 6.90; N, 7.46.

Example 175. Q^1=4-(N,N-Dimethylaminocarbonyl)-4-(2-oxopiperidino)-piperidino; MS: m/z=631(M+1). Analysis for $C_{33}H_{44}Cl_2N_4O_4{\bullet}0.40\ H_2O$: Calculated: C, 62.04; H, 7.07; N, 8.77; Found: C, 61.85; H, 6.86; N, 8.97.

Example 176. Q'=4-(Methylaminocarbonyl)-4-(2-oxopiperidino)piperidino; MS: m/z=617(M+1). Analysis for $C_{32}H_{42}Cl_2N_4O_4$•0.50 H_2O: Calculated: C, 61.34; H, 6.92; N, 8.94; Found: C, 61.14; H, 6.86; N, 9.16.

Example 177. Q'=4-(Carbamoyl)-4-piperidinipiperidino; MS: m/z=589(M+1). Analysis for $C_{31}H_{42}Cl_2N_4O_3$•1.0 H_2O•2.0 HCl: Calculated: C, 54.71; H, 6.81; N, 8.23; Found: C, 54.60; H, 6.64; N, 8.06.

Example 178. 3-(3,4-Dichlorophenyl)-5-(4-hydroxy-4-phenylpiperidino)-N-methyl-N-(2-methylphenyl)pentanamide.

Using a procedure similar to that described in Example 1, except replacing the benzylamine used therein with N-methyl-N-(2-methylphenyl)amine, the title compound was prepared; MS: m/z=509(M+1).

Example 179. 4-Acetamido-1-[3-(3,4-dichlorophenyl)-4-(N-(2-methoxybenzyl)-N-methylaminocarbonylbutyl]-1-methyl-4-phenylpiperidinium iodide.

N-Methyl-N-2-(methoxybenzyl)-5-(4-acetamido-4-phenylpiperidino)-3-(3,4-dichlorophenyl)pentanamide (the compound of Example 10, 0.075 g) was dissolved in dichloromethane (5 mL). Iodomethane (71 mg) was added. After 2 days at room temperature, the solution was evaporated. The resulting residue was triturated with ethyl ether to give the title compound (0.070 g); MS: m/z=611(M+1). Analysis for $C_{34}H_{42}Cl_2IN_3O_3$•0.65 H_2O: Calculated: C, 54.43; H, 5.82; N, 5.60; Found: C, 54.76; H, 5.79; N, 5.43.

Example 180. 4-Acetamido-1-[3-(3,4-dichlorophenyl)-4-(N-(2-methoxybenzyl)-N-methylaminocarbonylbutyl]-4-phenylpiperidine 1-oxide.

N-Methyl-N-2-(methoxybenzyl)-5-(4-acetamido-4-phenylpiperidino)-3-(3,4-dichlorophenyl)pentanamide (the compound of Example 10, 0.100 g) was dissolved in 5 mL dichloromethane and treated with meta-chloroperoxybenzoic acid (0.100 g) at room temperature. The mixture was stirred for 3 hours, evaporated and purified by column chromatography on neutral alumina, eluting first with dichloromethane and gradually increasing to 9:1 dichloromethane: methanol, to give the title compound (58 mg) as a

foamy solid; MS: m/z=612(M+1). Analysis for $C_{33}H_{39}Cl_2N_3O_4 \cdot 1.30\ H_2O$: Calculated: C, 62.32; H, 6.58; N, 6.61; Found: C, 62.12; H, 6.21; N, 6.71.

Examples 181-209

Using a procedure similar to that described in Example 173, except replacing the 2-oxoperhydropyrimidin-1-ylpiperidine with the requsite piperidine, the following compounds of formula I wherein Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen, Q^4 is N-(2-methoxybenzyl)-N-methylamino, and Q^1 is as defined were prepared.

Example 181. Q^1=4-Hydroxy-4-phenylpiperidino; MS: m/z=555(M+1).

Example 182. Q^1=4-Cyano-4-phenylpiperidino; MS: m/z=564(M+1).

Example 183. Q^1=4-Benzyl-4-hydroxypiperidino; MS: m/z=569(M+1).

Example 184. Q^1=4-(α-Hydroxy-a-Phenylbenzyl)piperidino; MS: m/z=645(M+1).

Example 185. Q^1=4-(N-Phenylpropionamido)piperidino; MS: m/z=610(M+1).

Example 186. Q^1=4-[N-(Aminocarbonylmethyl)aminocarbonyl]-4-(2-oxopiperidino)piperidino; MS: m/z=660(M+1).

Example 187. Q^1=4-(4-pyridyl)piperidino; MS: m/z=540(M+1).

Example 188. Q^1=4-(tert-Butoxycarbonylamino)piperidino; MS: m/z=578(M+1).

Example 189. Q^1=4-(phenoxymethyl)piperidino; MS: m/z=569(M+1).

Example 190. Q^1=a radical of formula Iv; MS: m/z=561(M+1).

Example 191. Q^1=4-[N-(2-methoxycarbonylethyl)aminocarbonyl]-4-(2-oxopiperidino)piperidino; MS: m/z=689(M+1).

Example 192. Q^1=9-Hydroxyperhydroisoquinol-2-yl; MS: m/z=533(M+1).

Example 193. Q^1=4-phenyl-4-(pyrrolidin-1-ylcarbonyl)piperidino; MS: m/z=636(M+1).

Example 194. Q'=4-Carboxy-4-phenylpiperidino; MS: m/z=583(M+1).

Example 195. Q'=4-Carboxy-4-(2-oxopiperidino)piperidino; MS: m/z=604(M+1).

Example 196. Q'=a radical of formula Ip wherein R^{pa} and R^{pb} are hydrogen; MS: m/z=565(M+1).

Example 197. Q'=Perhydroisoquinol-2-yl; MS: m/z=517(M+1).

Example 198. Q'=a radical of formula Iq wherein R^{qa} and R^{qd} are hydrogen and R^{qb} and R^{qc} are methoxy; MS: m/z=639(M+1).

Example 199. Q'=a radical of formula Ir; MS: m/z=547(M+1).

Example 200. Q'=4-(2-Oxo-1,2,3,4-tetrahydroquinazolin-3-yl)piperidino; MS: m/z=609(M+1).

Example 201. Q'=4-(Aminocarbonyl)-4-(N-ethylamino)piperidino; MS: m/z=549(M+1).

Example 202. Q'=4-(Acetamidomethyl)-4-phenylpiperidino; MS: m/z=610(M+1).

Example 203. Q'=4-aminocarbonyl-4-(N,N-dimethylamino)piperidino; MS: m/z=549(M+1).

Example 204. Q'=4-(Aminocarbonyl)-4-(N-isopropylamino)piperidino; MS: m/z=563(M+1).

Example 205. Q'=4-(Methoxycarbonyl)-4-(2-oxopiperidino)piperidino; MS: m/z=618(M+1).

Example 206. Q'=4-(2-Thioxopyrrolidin-1-yl)piperidino; MS: m/z=562(M+1).

Example 207. Q'=4-(Acetamido)piperidino; MS: m/z=520(M+1).

Example 208. Q'=4-(5,5-Dimethyl-2-oxoperhydropyrimidin-1-yl)piperidino; MS: m/z=589(M+1).

Examples 209-217

Using a procedure similar to that described in Example 16, except replacing the 1,2,3,4-tetrahydroisoquinoline with the requsite amine, the following compounds of formula I wherein Q^1 is 4-acetamido-4-phenylpiperidino, Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen and Q^4 is as defined, were prepared.

Example 209. Q^4= a radical of formula VII wherein E is oxy and m is 2; MS: m/z=608(M+1). Analysis for $C_{34}H_{39}Cl_2N_3O_3$•1.40 H_2O•1.00 HCl: Calculated: C, 60.92; H, 6.44; N, 6.27; Found; C, 60.81; H, 6.43; N, 6.27.

Example 210. Q^4=(R)-β-Methoxycarbonyl-4-hydroxyphenethylamino; MS: m/z=640(M+1).

Example 211. Q^4=(5-phenylpyrazol-3-yl)amino; MS: m/z=604(M+1).

Example 212. Q^4=4-(2-oxopiperidino)piperidino; MS: m/z=627(M+1).

Example 213. Q^4=4-(2-Oxoperhydropyrimidin-1-yl)piperidino; MS: m/z=628(M+1).

Example 214. Q^4=(1-Benzyl-4-hydroxymethylpiperidin-4-yl)amino; MS: m/z=665(M+1).

Example 215. Q^4=4-(tert-Butoxycarbonylamino)piperidino; MS: m/z=645(M+1).

Example 216. Q^4=4-Acetamido-4-phenylpiperidino; MS: m/z=663(M+1).

Example 217. N-Benzyl-5-(4-hydroxy-4-phenylpiperidino)-3-(3,4-dichlorophenyl)-N-methylpentanamide hydrochloride salt.

Using a procedure similar to that described in Example 1, except replacing the benzylamine used therein with N-benzyl-N-methylamine followed by conversion of the free amine to the hydrochloride salt as described in Example 2, the title compound was prepared; MS: m/z=525(M+1). Analysis for $C_{30}H_{34}Cl_2N_2O_2$•0.5 H_2O•1.0 HCl: Calculated: C, 63.10; H, 6.35; N, 4.90; Found: C, 63.02; H, 6.22; N, 4.86.

Examples 218-227

Using a procedure similar to that described in Example 173. except replacing the 2-oxoperhydropyrimidin-1-ylpiperidine with the requsite piperazine, the following compounds of formula I wherein Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen , Q^4 is N-(2-methoxybenzyl)-N-methylamino. and Q^1 is as defined were prepared

Example 218. Q^1=4-(2-pyridyl)piperazin-1-yl; MS: m/z=541(M+1).

Example 219. Q^1=4-(furan-2-ylcarbonyl)piperazin-1-yl; MS: m/z=558(M+1).

Example 220. Q^1=4-(2-fluorophenyl)piperazin-1-yl; MS: m/z=558(M+1).

Example 221. Q^1=4-(4-methoxyphenyl)piperazin-1-yl; MS: m/z=(570M+1).

Example 222. Q^1=4-(4-pyridyl)piperazin-1-yl; MS: m/z=541(M+1).

Example 223. Q^1=4-(2-pyrazinyl)piperazin-1-yl; MS: m/z=542(M+1).

Example 224. Q^1=4-phenylpiperazin-1-yl; MS: m/z=540(M+1).

Example 225. Q^1=4-(2-methoxyphenyl)piperazin-1-yl; MS: m/z=570(M+1).

Example 226. Q^1=4-(3-trifluoromethylphenyl)piperazin-1-yl; MS: m/z=608(M+1).

Example 227. Q^1=4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl; MS: m/z=575(M+1).

Examples 228-237

Using a procedure similar to that described in Example 173, except replacing the 2-oxoperhydropyrimidin-1-ylpiperidine with the requsite piperidine, and replacing the 3-(3,4-dichlorophenyl)-N-(2-methoxybenzyl)-N-methyl-5-oxopentanamide used therein with an aldehyde of formula XI, the following compounds of formula I wherein Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen , Q^4 is a radical of formula VII wherein E is oxy and m is 2, and Q^1 is as defined were prepared

Example 228. Q^1=4-(2-Oxoperhydropyrimidin-1-yl)piperidino; MS: m/z=573(M+1).

Example 229. Q^1=4-(2-Methylsulfinylphenyl)piperidino; MS: m/z=613(M+1).

Example 230. Q^1=4-Carbamoyl-4-(piperidino)piperidino; MS: m/z=601(M+1).

Example 231. Q^1=4-Hydroxy-4-phenylpiperidino; MS: m/z=567(M+1).

Example 232. Q^1=4-(2-Oxo-2,3-dihydrobenzimidazol-1-yl)piperidino; MS: m/z=607(M+1).

Example 233. Q^1=4-Carbamoyl-4-(N,N-dimethylamino)piperidino; MS: m/z=561(M+1).

Example 234. Q^1=4-Acetamido-4-phenylpiperidino; MS: m/z=608(M+1).

Example 235. Q^1=4-[(S*)-2-methylsulfinylphenyl]piperidino (see example66 for preparation of starting material); MS: m/z=613(M+1).

Example 236. Q^1=4-(Methylaminocarbonyl)-4-(2-oxopiperidino)piperidino; MS: m/z=629(M+1).

Example 237. Q^1=4-(2-Oxopiperidino)piperidino; MS: m/z=572(M+1).

Examples 238 and 239

Using a procedure similar to that described in Example 10, except replacing the N-methyl-N-(2-methoxybenzyl)amine with the requsite amine, the following compounds of formula I wherein Q^1 is 4-acetamido-4-phenylpiperidino, Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen and Q^4 is as defined were prepared.

Example 238. Q^4=N-(3,5-dichloro-2-methoxybenzyl)-N-methylamino; MS: m/z=665(M+1).

Example 239. Q^4=N-(3,5-dichloro-2-methoxybenzyl)amino; MS: m/z=651(M+1).

Examples 240-249

Using procedures similar to those described hereinabove. the following compounds of formula I wherein Q^2 is 3.4-dichlorophenyl, Q^3 is hydrogen , Q^4 is a radical of formula VII wherein E is oxy and m is 2. and Q^1 is as defined can be prepared.

Example 240. Q^1=4-(2-Oxoperhydropyrimidin-1-yl)piperidino.

Example 241. Q^1=4-(2-Methylsulfinylphenyl)piperidino.

Example 242. Q^1=4-Carbamoyl-4-(piperidino)piperidino.

Example 243. Q^1=4-Hydroxy-4-phenylpiperidino.

Example 244. Q^1=4-(2-Oxo-2.3-dihydrobenzimidazol-1-yl)piperidino.

Example 245. Q^1=4-Carbamoyl-4-(N.N-dimethylamino)piperidino.

Example 246. Q^1=4-Acetamido-4-phenylpiperidino.

Example 247. Q^1=4-[(S*)-2-methylsulfinylphenyl]piperidino (see example 66 for preparation of starting material).

Example 248. Q^1=4-(Methylaminocarbonyl)-4-(2-oxopiperidino)piperidino.

Example 249. Q^1=4-(2-Oxopiperidino)piperidino.

Examples 250-259

Using procedures similar to those described hereinabove, the following compounds of formula I wherein Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen , Q^4 is 6-chloro-chroman-4-ylamino, and Q^1 is as defined can be prepared.

Example 250. Q^1=4-(2-Oxoperhydropyrimidin-1-yl)piperidino.

Example 251. Q^1=4-(2-Methylsulfinylphenyl)piperidino.

Example 252. Q^1=4-Carbamoyl-4-(piperidino)piperidino.

Example 253. Q^1=4-Hydroxy-4-phenylpiperidino.

Example 254. Q^1=4-(2-Oxo-2.3-dihydrobenzimidazol-1-yl)piperidino.

Example 255. Q^1=4-Carbamoyl-4-(N,N-dimethylamino)piperidino.

Example 256. Q^1=4-Acetamido-4-phenylpiperidino.

Example 257. Q^1=4-[(S*)-2-methylsulfinylphenyl]piperidino (see example 66 for preparation of starting material).

Example 258. Q^1=4-(Methylaminocarbonyl)-4-(2-oxopiperidino)piperidino.

Example 259. Q^1=4-(2-Oxopiperidino)piperidino.

Examples 260-269

Using procedures similar to those described hereinabove, the following compounds of formula I wherein Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen , Q^4 is 1,2,3,4-tetrahydronaphth-1-ylamino. and Q^1 is as defined can be prepared.

Example 260. Q^1=4-(2-Oxoperhydropyrimidin-1-yl)piperidino.

Example 261. Q^1=4-(2-Methylsulfinylphenyl)piperidino.

Example 262. Q^1=4-Carbamoyl-4-(piperidino)piperidino.

Example 263. Q^1=4-Hydroxy-4-phenylpiperidino.

Example 264. Q^1=4-(2-Oxo-2,3-dihydrobenzimidazol-1-yl)piperidino.

Example 265. Q^1=4-Carbamoyl-4-(N,N-dimethylamino)piperidino.

Example 266. Q^1=4-Acetamido-4-phenylpiperidino.

Example 267. Q^1=4-[(S*)-2-methylsulfinylphenyl]piperidino (see example 66 for preparation of starting material).

Example 268. Q^1=4-(Methylaminocarbonyl)-4-(2-oxopiperidino)piperidino.

Example 269. Q^1=4-(2-Oxopiperidino)piperidino.

Examples 270-279

Using procedures similar to those described hereinabove. the following compounds of formula I wherein Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen , Q^4 is N-(chroman-4-yl)-N-methylamino. and Q^1 is as defined can be prepared.

Example 270. Q^1=4-(2-Oxoperhydropyrimidin-1-yl)piperidino.

Example 271. Q^1=4-(2-Methylsulfinylphenyl)piperidino.

Example 272. Q^1=4-Carbamoyl-4-(piperidino)piperidino.

Example 273. Q^1=4-Hydroxy-4-phenylpiperidino.

Example 274. Q^1=4-(2-Oxo-2.3-dihydrobenzimidazol-1-yl)piperidino.

Example 275. Q^1=4-Carbamoyl-4-(N,N-dimethylamino)piperidino.

Example 276. Q^1=4-Acetamido-4-phenylpiperidino.

Example 277. Q^1=4-[(S*)-2-methylsulfinylphenyl]piperidino (see example 66 for preparation of starting material).

Example 278. Q^1=4-(Methylaminocarbonyl)-4-(2-oxopiperidino)piperidino.

Example 279. Q^1=4-(2-Oxopiperidino)piperidino.

Examples 280-289

Using procedures similar to those described hereinabove, the following compounds of formula I wherein Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen , Q^4 is 2-fluorobenzylamino, and Q^1 is as defined can be prepared.

Example 280. Q^1=4-(2-Oxoperhydropyrimidin-1-yl)piperidino.

Example 281. Q^1=4-(2-Methylsulfinylphenyl)piperidino.

Example 282. Q^1=4-Carbamoyl-4-(piperidino)piperidino.

Example 283. Q^1=4-Hydroxy-4-phenylpiperidino.

Example 284. Q^1=4-(2-Oxo-2,3-dihydrobenzimidazol-1-yl)piperidino.

Example 285. Q^1=4-Carbamoyl-4-(N,N-dimethylamino)piperidino.

Example 286. Q^1=4-Acetamido-4-phenylpiperidino.

Example 287. Q^1=4-[(S*)-2-methylsulfinylphenyl]piperidino (see example 66 for preparation of starting material).

Example 288. Q^1=4-(Methylaminocarbonyl)-4-(2-oxopiperidino)piperidino.

Example 289. Q^1=4-(2-Oxopiperidino)piperidino.

Examples 290-299

Using procedures similar to those described hereinabove, the following compounds of formula I wherein Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen , Q^4 is 4-acetyl-4-phenylpiperidino, and Q^1 is as defined can be prepared.

Example 290. Q^1=4-(2-Oxoperhydropyrimidin-1-yl)piperidino.

Example 291. Q^1=4-(2-Methylsulfinylphenyl)piperidino.

Example 292. Q^1=4-Carbamoyl-4-(piperidino)piperidino.

Example 293. Q^1=4-Hydroxy-4-phenylpiperidino.

Example 294. Q^1=4-(2-Oxo-2,3-dihydrobenzimidazol-1-yl)piperidino.

Example 295. Q^1=4-Carbamoyl-4-(N,N-dimethylamino)piperidino.

Example 296. Q^1=4-Acetamido-4-phenylpiperidino.

Example 297. Q^1=4-[(S*)-2-methylsulfinylphenyl]piperidino (see example 66 for preparation of starting material).

Example 298. Q^1=4-(Methylaminocarbonyl)-4-(2-oxopiperidino)piperidino.

Example 299. Q^1=4-(2-Oxopiperidino)piperidino.

Examples 300-309

Using procedures similar to those described hereinabove, the following compounds of formula I wherein Q^2 is 3.4-dichlorophenyl, Q^3 is hydrogen , Q^4 is 2-indanyl, and Q^1 is as defined can be prepared.

Example 300. Q^1=4-(2-Oxoperhydropyrimidin-1-yl)piperidino.

Example 301. Q^1=4-(2-Methylsulfinylphenyl)piperidino.

Example 302. Q^1=4-Carbamoyl-4-(piperidino)piperidino.

Example 303. Q^1=4-Hydroxy-4-phenylpiperidino.

Example 304. Q^1=4-(2-Oxo-2.3-dihydrobenzimidazol-1-yl)piperidino.

Example 305. Q^1=4-Carbamoyl-4-(N,N-dimethylamino)piperidino.

Example 306. Q^1=4-Acetamido-4-phenylpiperidino.

Example 307. Q^1=4-[(S*)-2-methylsulfinylphenyl]piperidino (see example 66 for preparation of starting material).

Example 308. Q^1=4-(Methylaminocarbonyl)-4-(2-oxopiperidino)piperidino.

Example 309. Q^1=4-(2-Oxopiperidino)piperidino.

Examples 310-319

Using procedures similar to those described hereinabove, the following compounds of formula I wherein Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen , Q^4 is 3,4-dichloro-2-methoxybenzyl, and Q^1 is as defined can be prepared.

Example 310. Q^1=4-(2-Oxoperhydropyrimidin-1-yl)piperidino.

Example 311. Q^1=4-(2-Methylsulfinylphenyl)piperidino.

Example 312. Q^1=4-Carbamoyl-4-(piperidino)piperidino.

Example 313. Q^1=4-Hydroxy-4-phenylpiperidino.

Example 314. Q^1=4-(2-Oxo-2.3-dihydrobenzimidazol-1-yl)piperidino.

Example 315. Q^1=4-Carbamoyl-4-(N,N-dimethylamino)piperidino.

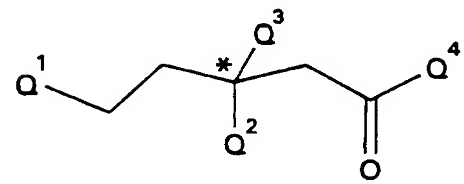
Example 316. Q^1=4-Acetamido-4-phenylpiperidino.

Example 317. Q^1=4-[(S*)-2-methylsulfinylphenyl]piperidino (see example 66 for preparation of starting material).

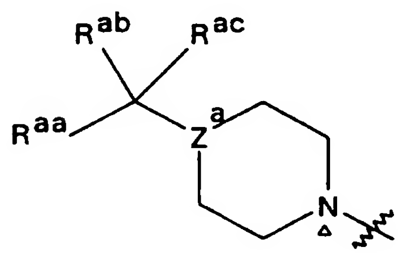
Example 318. Q^1=4-(Methylaminocarbonyl)-4-(2-oxopiperidino)piperidino.

Example 319. Q^1=4-(2-Oxopiperidino)piperidino.

FORMULAE



I



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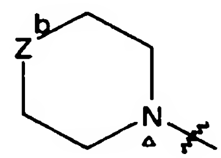

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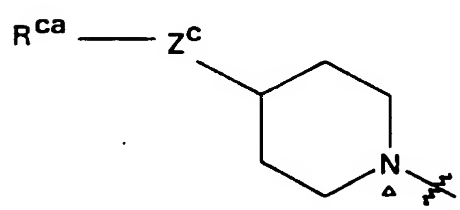

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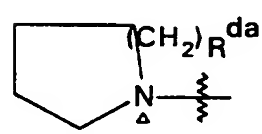

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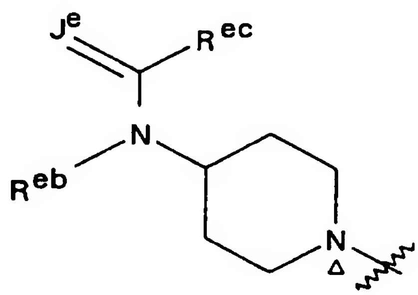

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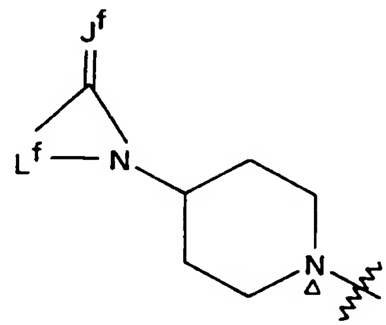

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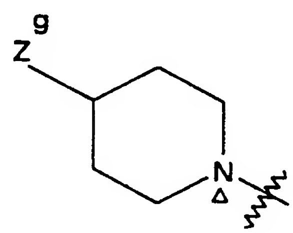

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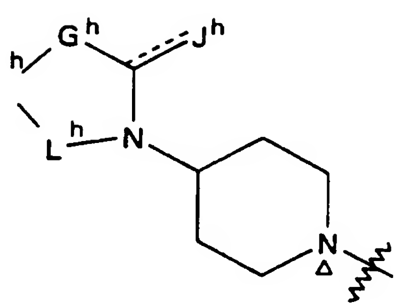

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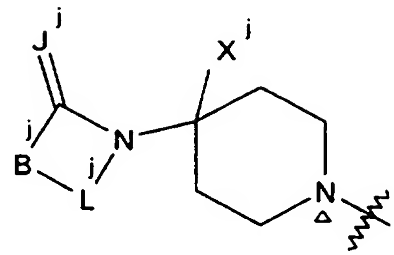

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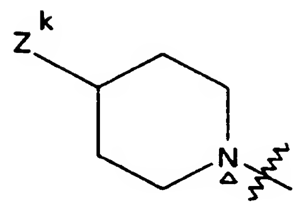

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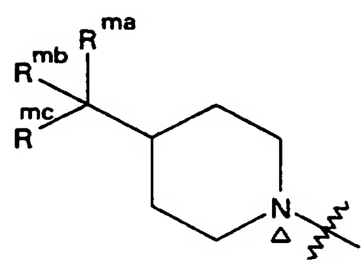

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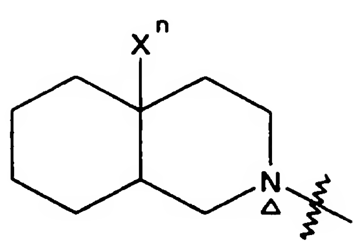

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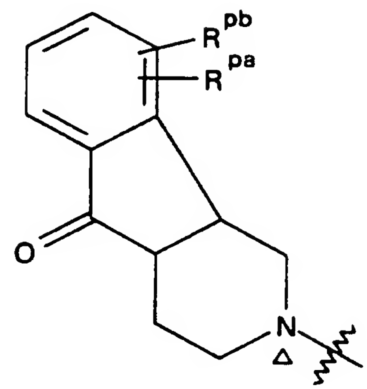

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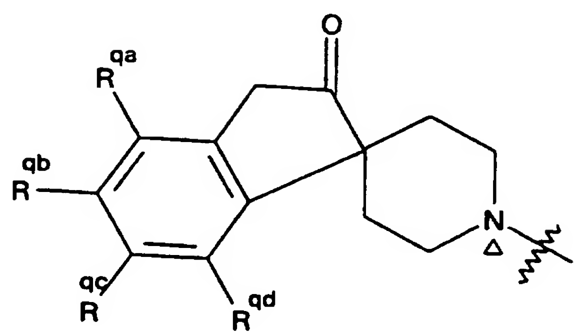

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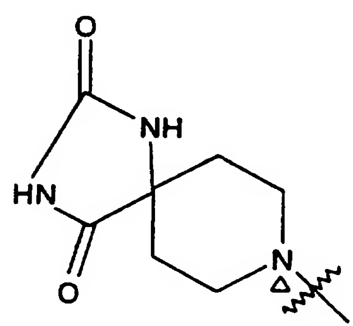

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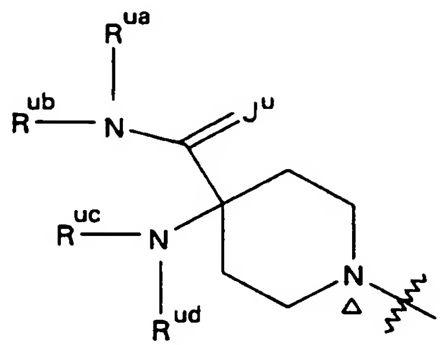

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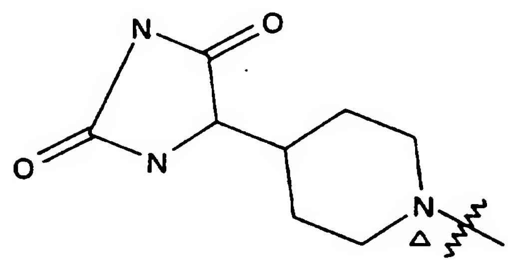

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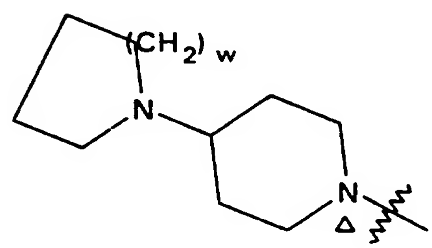

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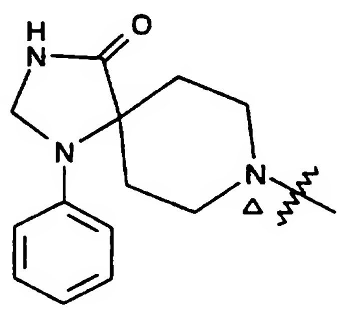

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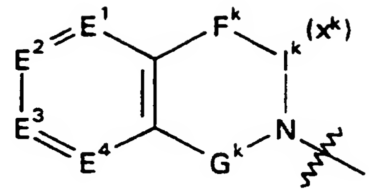

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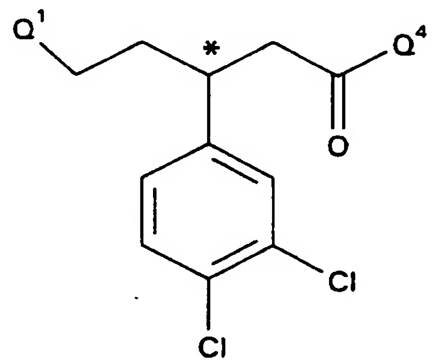

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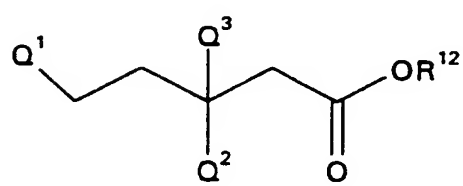

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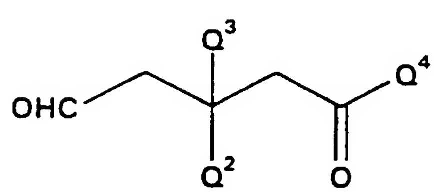

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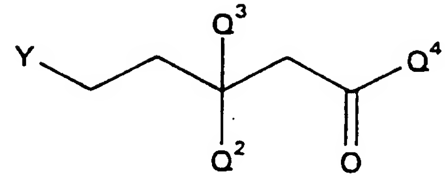

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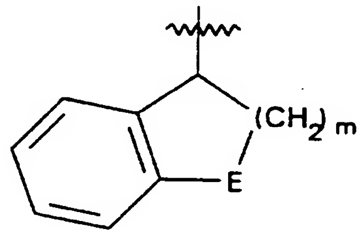

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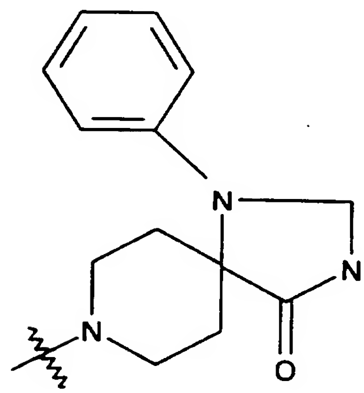

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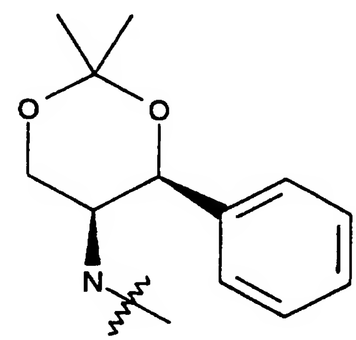

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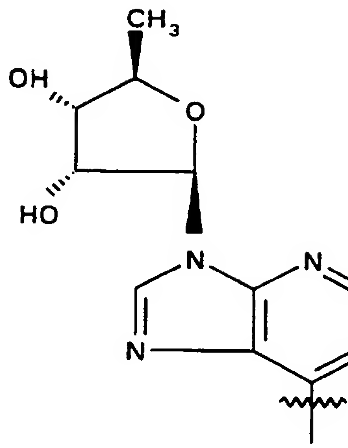

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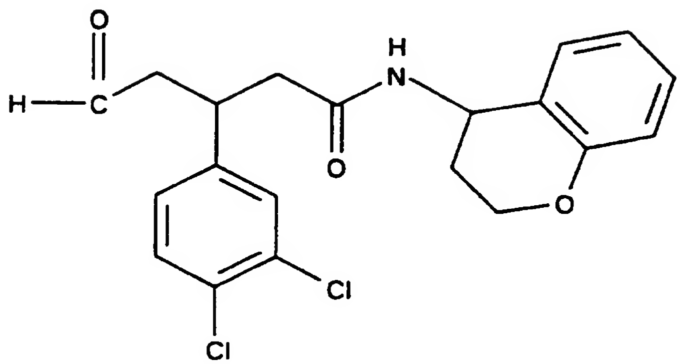
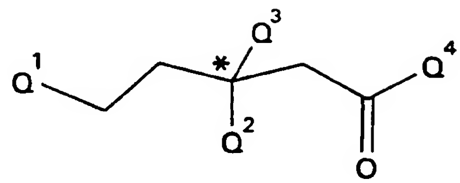


XI

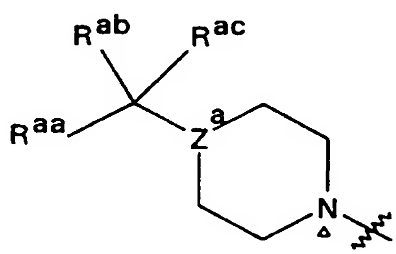
What is claimed is:

1. A compound of formula I:

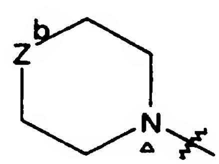


I

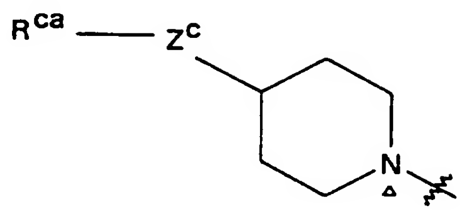
wherein Q^1 is a radical selected from the group of radicals of formulae Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ij, Ik, Im, In, Ip, Iq, Ir, Iu, Iv, Iw and Ix:



Ia



Ib



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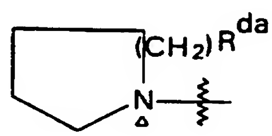

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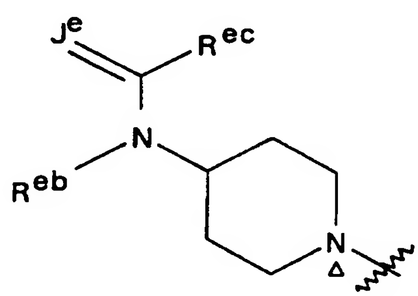

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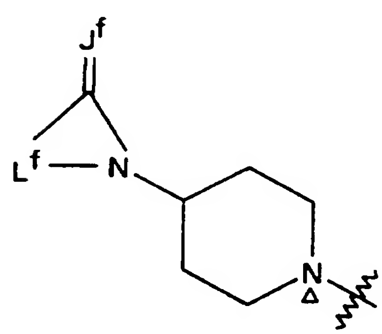

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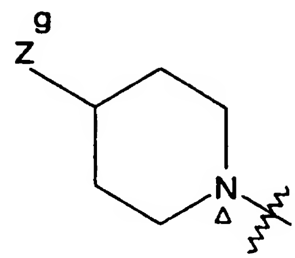

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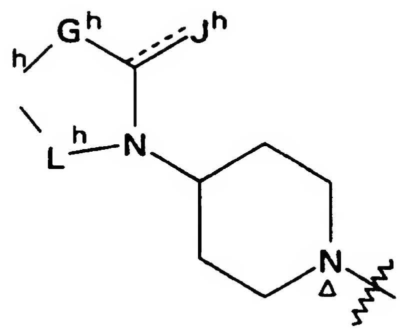

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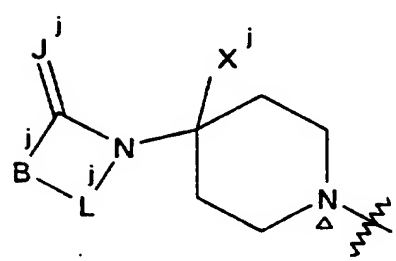

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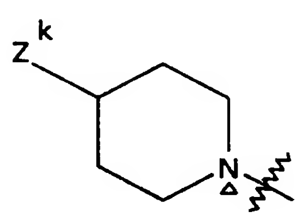

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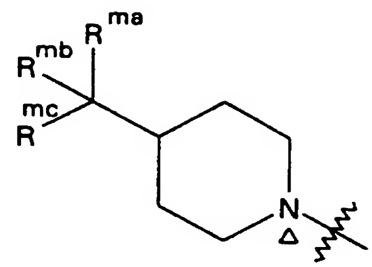

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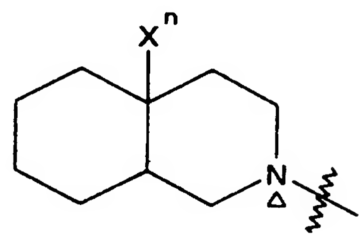

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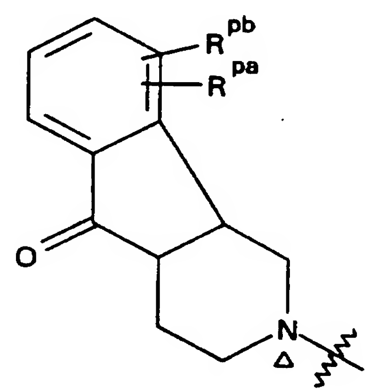

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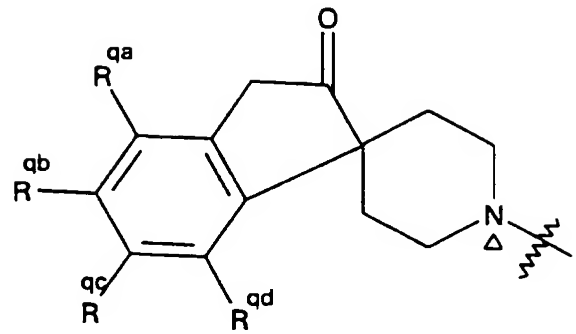

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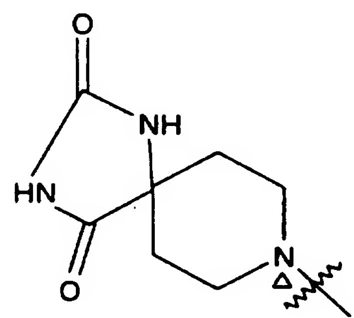

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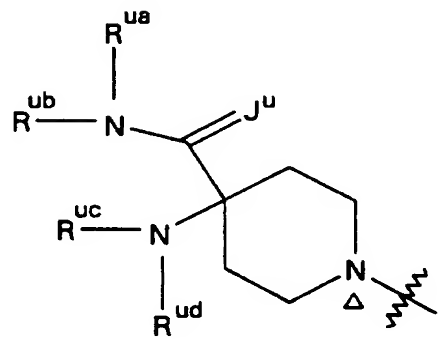
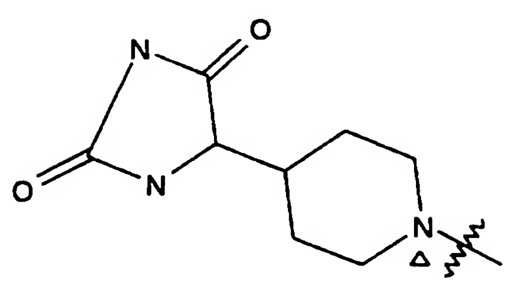


Iu



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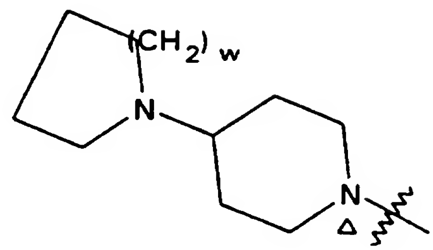

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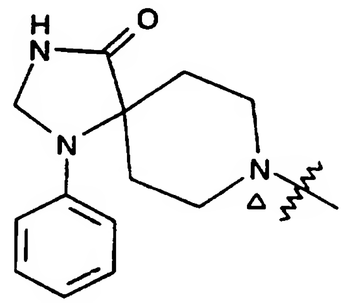


Ix

wherein

for a radical of formula Ia, Z^a is nitrogen or a group CR^{ad} in which R^{ad} is hydrogen or R^{ad} together with R^{ac} and the existing carbon to carbon bond forms a double bond; R^{aa} is Ar or Het; R^{ab} is hydrogen and R^{ac} is hydrogen or hydroxy or R^{ac} together with R^{ad} and the existing carbon to carbon bond forms a double bond, or R^{ac} and R^{ad} together form a diradical $-(CH_2)_j-$ in which j is an integer from 1 to 5; or R^{ab} and R^{ac} together form a diradical $-(CH_2)_k-$ in which k is an integer from 2 to 6, or R^{ab} and R^{ac} together are oxo or dialkylaminoalkyloxyimino of formula $=N-O-(CH_2)_q-NR^{ae}R^{af}$ in which q is the integer 2 or 3 and R^{ae} and R^{af} are independently hydrogen or (1-4C)alkyl, or the radical $NR^{ae}R^{af}$ is pyrrolidino, piperidino or morpholino;

for a radical of formula Ib, Z^b is a substituted imino group $R^{ba}N$ or $R^{ba}CH_2N$ in which R^{ba} is (3-7C)cycloakyl, Ar, Het, Ar(carbonyl), Het(carbonyl), $CH_2\ NR^{be}R^{bf}$, $C(=O)NR^{be}R^{bf}$, $CH_2C(=O)NR^{be}R^{bf}$; or Z^b is a disubstituted methylene group $R^{bb}(CH_2)_p-C-R^{bc}$ in which R^{bb} is Ar or Het; p is the integer 0 or 1; and R^{bc} is hydrogen,

hydroxy, (1-4C)alkoxy, (1-4C)alkanoyloxy, $COOR^{bd}$ (wherein R^{bd} is hydrogen or (1-3C)alkyl), cyano, $CH_2 NR^{be}R^{bf}$, $C(=O)NR^{be}R^{bf}$, $NR^{be}R^{bf}$ or SR^{bg} in which R^{be} and R^{bf} are independently hydrogen, (1-4C)alkyl, (1-4C)hydroxyalkyl or (1-4C)alkanoyl, or the radical $NR^{be}R^{bf}$ is pyrrolidino, piperidino or morpholino; and R^{bg} is hydrogen or (1-4C)alkyl; or R^{bc} forms a double bond with the carbon atom to which it is bonded and with the adjacent carbon atom in the piperidine ring; or Z^b is a disubstituted methylene group $R^{bh}CR^{bi}$ which forms a spirocyclic ring wherein R^{bh} is phenyl which is joined by an ortho-substituent diradical X^b to R^{bi} in which the phenyl R^{bh} may bear a further substituent selected from halo, (1-3C)alkyl, (1-3C)alkoxy, hydroxy, (1-3C)alkylthio, (1-3C)alkylsulfinyl and (1-3C)alkylsulfonyl; the diradical X^b is methylene, carbonyl or sulfonyl; and R^{bi} is oxy or imino of formula $-NR^{bj}-$ in which R^{bj} is hydrogen or (1-3C)alkyl;

for a radical of formula Ic, R^{ca} is Ar or Het; and Z^c is oxo, thio, sulfinyl, sulfonyl or imino of formula $-NR^{cb}-$ in which R^{cb} is (1-3C)alkyl or $R^{cc}R^{cd}N-(CH_2)_q-$ in which q is the integer 2 or 3 and in which R^{cc} and R^{cd} are independently hydrogen or (1-3C)alkyl or the radical $R^{cc}R^{cd}N$ is pyrrolidino, piperidino or morpholino;

for a radical of formula Id, R^{da} is 1, 2 or 3;

for a radical of formula Ie, J^e is oxygen, sulfur or NR^{ea} in which R^{ea} is hydrogen or (1-3C)alkyl; R^{eb} is hydrogen, (1-6C)alkyl which may bear a hydroxy substituent and/or one to three fluoro substituents, (3-6C)alkenyl (in which a vinyl carbon is not bound to nitrogen), 2-hydroxyethyl, (3-7C)cyloalkyl, Ar or Het; R^{ec} is hydrogen, (1-6C)alkyl which may bear a hydroxy substituent and/or one to three fluoro substituents, (3-6C)cycloalkyl, (1-5C)alkoxy (only when J^e is oxygen), (3-6C)cycloalkoxy (only when J^e is oxygen), or an amino group of formula $NR^{ed}R^{ee}$ containing zero to seven carbon atoms in which each of R^{ed} and R^{ee} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{ed}R^{ee}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl group may bear a (1-3C)alkyl substituent at the 4-position);

for a radical of formula If, J^f is oxygen, sulfur or NR^{fa} in which R^{fa} is hydrogen or (1-3C)alkyl; L^f is a divalent hydrocarbon group in which the 1-position is bound to the

carbon bearing the group J^f, the divalent group L^f being selected from trimethylene, cis-propenylene, tetramethylene, cis-butenylene, cis-but-3-enylene, cis,cis-butadienylene, pentamethylene and cis-pentenylene which divalent group L^f itself may bear one or two methyl substituents;

for a radical of formula Ig, Z^g is (1-8C)alkyl or (3-8C)cycloalkyl which may bear one or more substituents selected from the group consisting of halo, (3-6C)cycloalkyl, cyano, nitro, hydroxy, (1-4C)alkoxy, (1-5C)alkanoyloxy, aroyl, heteroaroyl, oxo, imino (which may bear a (1-6C)alkyl, (3-6C)cycloalkyl, (1-5C)alkanoyl or aroyl substituent), hydroxyimino (which hydroxyimino may bear a (1-4C)alkyl or a phenyl substituent on the oxygen), an amino group of formula $NR^{ga}R^{gb}$, an amino group of formula $NR^{gc}R^{gd}$, an amidino group of formula $C(=NR^{gg})NR^{ge}R^{gf}$, and a carbamoyl group of formula $CON(OR^{gh})R^{gi}$, but excluding any radical wherein a hydroxy and an oxo substituent together form a carboxy group, wherein an amino group of formula $NR^{ga}R^{gb}$ contains zero to seven carbon atoms and each of R^{ga} and R^{gb} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{ga}R^{gb}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent group at the 4-position); and wherein R^{gc} is hydrogen or (1-3C)alkyl and R^{gd} is (1-5C)alkanoyl, aroyl or heteroaroyl; or R^{gd} is a group of formula $C(=J^g)NR^{ge}R^{gf}$ in which J^g is oxygen, sulfur, NR^{gg} or CHR^{gj}; and wherein the amino group $NR^{ge}R^{gf}$ contains zero to seven carbon atoms and each of R^{ge} and R^{gf} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{ge}R^{gf}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position) or R^{ge} is hydrogen or (1-4C)alkyl and R^{gf} together with R^{gg} forms an ethylene or trimethylene group; R^{gg} is hydrogen, (1-4C)alkyl or together with R^{gf} forms an ethylene or trimethylene group; R^{gj} is cyano, nitro or SO_2R^{gk} and R^{gk} is (1-4C)alkyl or phenyl; R^{gh} and R^{gi} are independently (1-3C)alkyl; and in which a cyclic group which is a substituent on Z^g or formed by substitution on Z^g may bear one or more (1-3C)alkyl groups on carbon as further substituents; and in which any aryl or heteroaryl group which is a part of the group Z^g may bear one or more halo, (1-4C)alkyl, (1-4C)alkoxy, cyano, trifluoromethyl or nitro substituents;

for a radical of formula Ih, G^h denotes a single bond, a double bond or a divalent hydrocarbon radical: J^h denotes a radical joined to the ring by a single bond if G^h denotes a double bond or, otherwise, a radical joined by a double bond; M^h denotes a heteroatom, a substituted heteroatom, or a single bond: and L^h denotes a hydrocarbon radical in which the 1-position is attached to M^h; wherein the values of G^h, J^h, M^h and L^h are selected from

(a) G^h is a single bond: J^h is oxo or thioxo; M^h is oxy, thio or NR^{ha}; and L^h is L^{ha};

(b) G^h is a single bond; J^h is NR^{hb}; M^h is NR^{ha}; and L^h is L^{ha};

(c) G^h is a double bond, J^h is OR^{ha}, SR^{ha} or $NR^{hc}R^{hd}$; M^h is nitrogen: and L^h is L^{ha};

(d) G^h is methylene which may bear one or two methyl substituents: J^h is oxo, thioxo or NR^{he}; M^h is oxy, thio, sulfinyl, sulfonyl or NR^{ha}; and L^h is L^{hb};

(e) G^h is a single bond; J^h is oxo, thioxo or NR^{he}; M^h is nitrogen: and L^h is L^{hc};

(f) G^h is methine, which may bear a (1-3C)alkyl substituent; J^h is oxo, thioxo or NR^{he}; M^h is nitrogen; and L^h is L^{hd};

(g) G^h is cis-vinylene, which may bear one or two methyl substituents; J^h is oxo, thioxo, or NR^{he}; M^h is nitrogen: and L^h is L^{he}; and

(h) G^h is a single bond; J^h is oxo or thioxo; M^h is a single bond; and L^h is L^{hf}; wherein

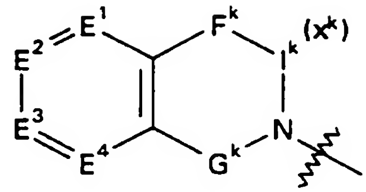
R^{ha} is hydrogen or (1-3C)alkyl; R^{hb} is hydrogen, (1-3C)alkyl, cyano, (1-3C)alkylsulfonyl or nitro; R^{hc} and R^{hd} are independently hydrogen or (1-3C)alkyl or the radical $NR^{hc}R^{hd}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{he} is hydrogen or (1-3C)alkyl; L^{ha} is ethylene, cis-vinylene, trimethylene or tetramethylene which radical L^{ha} itself may bear one or two methyl substituents; L^{hb} is ethylene or trimethylene which radical L^{hb} itself may bear one or two methyl substituents; L^{hc} is

prop-2-en-1-yliden-3-yl, which radical L^{hc} itself may bear one or two methyl substituents; L^{hd} is cis-vinylene, which radical L^{hd} itself may bear one or two methyl substituents; L^{he} is methine, which radical L^{he} itself may bear a (1-3C)alkyl substituent; and L^{hf} is 4-oxabutan-1,4-diyl;

for a radical of formula Ij, X^j is (1-6C)alkyl, $-CH_2OR^{ja}$, $-CH_2SR^{ja}$, $-CH_2S(O)R^{jg}$, $-CH_2S(O)_2R^{jg}$, $-COR^{ja}$, $-COOR^{ja}$, $-C(=J^{ja})NR^{jb}R^{jc}$, $-C(R^{ja})(OR^{jd})(OR^{je})$, $-CH_2N(R^{ja})C(=J^{ja})R^{jf}$, $-CH_2N(R^{ja})COOR^{jg}$ or $-CH_2N(R^{ja})C(=J^{ja})NR^{jb}R^{jc}$;

B^j is a direct bond and L^j is a hydrocarbon chain in which the 1-position is bound to B^j and L^j is selected from trimethylene, tetramethylene, cis-1-butenylene and cis,cis-butadienylene; or B^j is $N(R^{jh})$ and L^j is a hydrocarbon chain selected from ethylene, trimethylene and cis-vinylene; or B^j is N and L^j is a hydrocarbon chain in which the 1-position is bound to B^j and L^j is cis,cis-prop-2-en-1-ylidin-3-yl; J^j and J^{ja} are independently oxygen or sulfur; R^{ja}, R^{jf} and R^{jh} are independently hydrogen or (1-6C)alkyl; R^{jb} and R^{jc} are independently hydrogen or (1-6C)alkyl; or the radical $NR^{jb}R^{jc}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{jd} and R^{je} are independently (1-3C)alkyl or together form a divalent hydrocarbon chain selected from ethylene and trimethylene; R^{jg} is (1-6C)alkyl; wherein any (1-6C)alkyl radical in a portion of X^j may substituted by one or two substituents selected from hydroxy, (1-3C)alkoxy, (1-3C)acyloxy, (1-3C)alkoxycarbonyl, $NR^{jh}R^{ji}$, and $C(=O)NR^{jh}R^{ji}$, wherein R^{jh} and R^{ji} are independently hydrogen, (1-4C)alkyl, (1-4C)hydroxyalkyl or (1-4C)alkanoyl, or the group $NR^{jh}R^{ji}$ is pyrrolidino, piperidino or morpholino;

for a radical of formula Ik, Z^k is a nitrogen linked radical of formula II:



II

wherein E^1, E^2, E^3 and E^4 form a divalent four membered chain ($-E^1=E^2-E^3=E^4-$) in which each of E^1, E^2, E^3 and E^4 is methine; or in which one or two of E^1, E^2, E^3 and E^4 is nitrogen and the remaining E^1, E^2, E^3 and E^4 are methine; and further wherein one or more of E^1, E^2, E^3 and E^4 which is methine may bear a halo, (1-3C)alkyl, hydroxy, (1-3C)alkoxy, (1-3C)alkylthio, (1-3C)alkylsulfinyl or (1-3C)alkylsulfonyl substituent; and wherein the radicals F^k, G^k, and $I^k(X^k)$ are selected from

(a) G^k is a direct bond, $I^k(X^k)$ is a radical having the formula $=C(Z^k)-$ and F^k is a radical selected from -CH= and -N=;

(b) G^k is a direct bond, $I^k(X^k)$ is a radical having the formula $-C(=J^k)-$ and F^k is a radical selected from $-N(R^{kf})-$, $-CH_2-CH_2-$, -CH=CH-, $-CH_2-N(R^{kf})-$ and -CH=N-;

(c) G^k is a radical having the formula $-CH_2-$, $I^k(X^k)$ is a radical having formula $-C(=J^k)-$ and F^k is selected from $-CH_2-$ and $-N(R^{kf})-$; and

(d) G^k is selected from $-CH_2-$, $-CH_2-CH_2-$, -CH=CH- and -N=CH-, $I^k(X^k)$ is a radical having the formula $-C(=J^k)-$ and F^k is a direct bond; wherein

J^k is oxygen or sulfur; Z^k is $-OR^{ka}$, $-SR^{ka}$, $-COR^{ka}$, $-COOR^{ka}$, $-C(=J^{ka})NR^{kb}R^{kc}$ or $-C(R^{ka})(OR^{kd})(OR^{ke})$; J^{ka} is oxygen or sulfur; R^{ka} and R^{kf} are independently hydrogen or (1-6C)alkyl; R^{kb} and R^{kc} are independently hydrogen or (1-6C)alkyl; or the radical $NR^{kb}R^{kc}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{kd} and R^{ke} are independently (1-3C)alkyl or R^{kd} and R^{ke} together form ethylene or trimethylene; or Z^k is an imido radical selected from phthalimido, succinimido, maleimido, glutarimido, and 3-oxa-, 3-thia- and 3-azaglutarimido, in which the imido radical may bear one or more (1-3C)alkyl

substituents and. in addition. the aromatic portion of the phthalimido may bear one or more halo. hydroxy or (1-3C)alkoxy substituents:

for a radical of formula Im. R^{ma} and R^{mb} are Ar or Het and R^{mc} is selected from hydroxy, (1-3C)alkoxy, and (1-3C)acyloxy; or R^{ma} is (Ar)oxy, or (Het)oxy. and R^{mb} and R^{mc} are hydrogen;

for a radical of formula In. X^n is selected from hydrogen, hydroxy, (1-3C)alkoxy and (1-3C)acyloxy;

for a radical of formula Ip. R^{pa} and R^{pb} are independently selected from hydrogen, hydroxy, (1-3C)alkoxy, (1-3C)acyloxy, halo. cyano. and trifluoromethyl;

for a radical of formula Iq. R^{qa}-R^{qd} are are independently selected from hydrogen. hydroxy. (1-3C)alkoxy, (1-3C)acyloxy, halo. cyano. and trifluoromethyl;

for a radical of formula Iu. Ju is oxygen or sulfur; and R^{ua}-R^{ud} are independently selected from hydrogen, (1-4C)alkyl, (1-4C)hydroxyalkyl and (1-4C)alkanoyl, or the group $NR^{ua}R^{ub}$ or the group $NR^{uc}R^{ud}$ is pyrrolidino, piperidino or morpholino;

for a radical of formula Iw, w is 1, 2. or 3; and wherein

for a radical Q^1, Ar is a phenyl radical or an ortho-fused bicyclic carbocyclic radical of nine of ten ring atoms in which at least one ring is aromatic, which radical Ar may be unsubstituted or may bear one or more substituents selected from halo, cyano, trifluoromethyl, (1-4C)alkyl, (1-4C)alkoxy, methylenedioxy, hydroxy, mercapto, $-S(O)_nR^{xa}$, (1-5C)alkanoyl, (1-5C)alkanoyloxy, nitro, $NR^{xb}R^{xc}$, $NR^{xd}R^{xe}$, $C(=NR^{xf})NR^{xg}R^{xh}$, $CONR^{xb}R^{xc}$ and $COOR^{xj}$ wherein n is the integer 0, 1, or 2; R^{xa} is (1-6C)alkyl, (3-6C)cycloalkyl or phenyl (which phenyl may bear a halo, trifluoromethyl, (1-3C)alkyl or (1-3C)alkoxy substitutent); the radical $NR^{xb}R^{xc}$ contains zero to seven carbons and each of R^{xb} and R^{xc} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{xb}R^{xc}$ is pyrrolidino, piperidino, morpholino, thiomorpholine (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); and wherein R^{xd} is hydrogen or (1-4C)alkyl and R^{xe} is (1-5C)alkanoyl, benzoyl; or a group of

formula $C(=J^x)NR^{xg}R^{xh}$ in which J^x is oxygen, sulfur, NR^{xf} or CHR^{xi}; R^{xf} is hydrogen, (1-5C)alkyl or together with R^{xg} forms an ethylene or trimethylene diradical, the radical $NR^{xg}R^{xh}$ contains zero to 7 carbons and each of R^{xg} amd R^{xh} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{xg}R^{xh}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); or R^{xg} together with R^{xf} forms an ethylene or trimethylene diradical and R^{xh} is hydrogen or (1-5C)alkyl; R^{xi} is cyano, nitro, (1-5C)alkylsulfonyl or phenylsulfonyl; and R^{xj} is hydrogen, (1-5C)alkyl or benzyl; and Het is a radical (or stable N-oxide thereof) attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms selected from oxygen, sulfur and nitrogen, or an ortho-fused bicyclic heterocycle derived therefrom by fusing a propenylene, trimethylene, tetramethylene or benz-diradical, which radical Het may be unsubstituted or may be substituted on carbon by one or more of the substituents defined above for Ar and may be substituted on nitrogen by (1-3C)alkyl;

Q^2 is phenyl which may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl and methylenedioxy; or Q^2 is thienyl, imidazolyl, benzo[b]thiophenyl or naphthyl any of which may bear a halo substituent; or Q^2 is biphenylyl; or Q^2 is carbon-linked indolyl which may bear a benzyl substituent at the 1-position;

Q^3 is hydrogen, or (1-4C)alkyl; and

Q^4 is $-OR^2$ or $-NR^3R^4$; wherein

R^2 is hydrogen, (1-6C)alkyl, (3-7C)cycloalkyl, aryl(1-3C)alkyl or heteroaryl(1-3C)alkyl, wherein an aryl or heteroaryl group may bear one, two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-S(=O)_2NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, and methylenedioxy, and further wherein any arylethyl, arylpropyl, heteroarylethyl or heteroarylpropyl group may optionally be substituted at the position a to the aryl or heteroaryl group by a group selected from oxo, and $=NOR^{11}$;

R^3 and R^4 are independently selected from hydrogen, (1-8C)alkyl, norbornyl, adamantyl, quinuclidinyl, (1-6C)alkoxy, (3-7C)cycloalkyl, pyrrolidinyl, tetrahydrofuranyl, piperidyl, 1-benzylpiperidyl, 4,5-dihydrothiazolyl, 3,4,5,6-tetrahydrophenyl, fluorenyl, 5-oxo-4,5-dihydropyrazol-3-yl, aryl, heteroaryl, arylsulfinyl, arylsulfonyl, heteroarylsulfinyl, heteroarylsulfonyl, 1-phenyl-4,5-dihydropyrazol-3-yl, 1-benzylpyrrolidin-3-yl, and a radical of formula VII; wherein (1-8C)alkyl may be substituted by one, two, or three substituents selected from, hydroxy, oxo, $=NOR^{11}$, amino, pyrrolidinyl, 1-methylpyrrolidinyl, piperidinyl, (1-3C)alkoxy, (1-4C)alkanoyl, (1-3C)alkoxycarbonyl, (3-7C)cycloalkyl, adamantyl, norbornyl, quinuclidinyl, tetrahydrofuranyl, 4,5-dihydrothiazolyl, 3,4,5,6-tetrahydrophenyl, fluorenyl, 5-oxo-4,5-dihydropyrazol-3-yl, aryl and heteroaryl; and further wherein any aryl or heteroaryl group, or radical of formula VII may bear one two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, (1-4C)alkanoyl, C(=O)OR5, $-S(=O)_2NR^5R^6$, $-S(=O)NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, and methylenedioxy; provided that R^3 and R^4 are not both selected from (1-6C)alkoxy; or

$-NR^3R^4$ taken together represents a cyclic amino radical selected from piperazinyl, pyrrolidinyl, piperidino, 1,2,3,6-tetrahydropyridyl, 1,2,3,4-tetrahydroquinolyl, and 1,2,3,4-tetrahydroisoquinolyl, which cyclic amino radical may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-4C)alkanoyl, (1-3C)alkyl, cyano, $-S(=O)^2NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, $CH_2N(R^7)C(=O)R^8$, pyrrolidinyl, 2-(thioxo)pyrrolidinyl, piperidinyl, pyridyl, morpholinocarbonyl, piperidinocarbonyl, 2-oxo-benzimidazolidin-1-yl, phenyl, benzyl, acetamidomethyl, and methylenedioxy; wherein any phenyl or phenyl portion of benzyl may optionally bear one, two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, or cyano; or

$-NR^3R^4$ taken together represents an amino radical selected from radicals of formulae VIII, IX, and X.

E is selected from -O-, -S-, $-N(R^{14})-$, -S(=O)- and $-S(O)_2-$;

m is 1 or 2; and

R^5-R^{11} are independently selected from hydrogen and (1-3C)alkyl

or the N-oxide of the nitrogen in Q^1 indicated by Δ in formulae Ia-Iv (or of either basic piperazinyl nitrogen of Q^1 when Z^a is nitrogen);

or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the nitrogen in Q^1 indicated by Δ in formulae Ia-Ix (or either basic piperazinyl nitrogen of Q^1 when Z^a is nitrogen) is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R^1 is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

2. A compound as claimed in claim 1 wherein Q^1 is a radical selected from the group of radicals of formulae Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ij and Ik wherein:

for a radical of formula Ia, Z^a is nitrogen or a group CR^{ad} in which R^{ad} is hydrogen or R^{ad} together with R^{ac} and the existing carbon to carbon bond forms a double bond; R^{aa} is Ar or Het; R^{ab} is hydrogen and R^{ac} is hydrogen or hydroxy or R^{ac} together with R^{ad} and the existing carbon to carbon bond forms a double bond, or R^{ac} and R^{ad} together form a diradical $-(CH_2)_j-$ in which j is an integer from 1 to 5; or R^{ab} and R^{ac} together form a diradical $-(CH_2)_k-$ in which k is an integer from 2 to 6, or R^{ab} and R^{ac} together are oxo or dialkylaminoalkyloxyimino of formula $=N-O-(CH_2)_q-NR^{ae}R^{af}$ in which q is the integer 2 or 3 and R^{ae} and R^{af} are independently hydrogen or (1-4C)alkyl, or the radical $NR^{ae}R^{af}$ is pyrrolidino, piperidino or morpholino;

for a radical of formula Ib, Z^b is a substituted imino group $R^{ba}N$ or $R^{ba}CH_2N$ in which R^{ba} is (3-7C)cycloakyl, Ar or Het; or Z^b is a disubstituted methylene group $R^{bb}(CH_2)_p$-C-R^{bc} in which R^{bb} is Ar or Het; p is the integer 0 or 1; and R^{bc} is hydrogen, hydroxy, (1-4C)alkoxy, (1-4C)alkanoyloxy, $COOR^{bd}$ (wherein R^{bd} is hydrogen or (1-3C)alkyl), cyano, $NR^{be}R^{bf}$ or SR^{bg} in which R^{be} and R^{bf} are independently hydrogen, (1-4C)alkyl, (1-4C)hydroxyalkyl or (1-4C)alkanoyl, or the radical $NR^{be}R^{bf}$ is pyrrolidino, piperidino or morpholino; and R^{bg} is hydrogen or (1-4C)alkyl; or R^{bc} forms a double bond with the carbon atom to which it is bonded and with the adjacent carbon atom in the

piperidine ring; or Z^b is a disubstituted methylene group $R^{bh}CR^{bi}$ which forms a spirocyclic ring wherein R^{bh} is phenyl which is joined by an ortho-substituent diradical X^b to R^{bi} in which the phenyl R^{bh} may bear a further substituent selected from halo, (1-3C)alkyl, (1-3C)alkoxy, hydroxy, (1-3C)alkylthio, (1-3C)alkylsulfinyl and (1-3C)alkylsulfonyl; the diradical X^b is methylene, carbonyl or sulfonyl; and R^{bi} is oxy or imino of formula $-NR^{bj}-$ in which R^{bj} is hydrogen or (1-3C)alkyl;

for a radical of formula Ic, R^{ca} is Ar or Het; and Z^c is oxo, thio, sulfinyl, sulfonyl or imino of formula $-NR^{cb}-$ in which R^{cb} is (1-3C)alkyl or $R^{cc}R^{cd}N-(CH_2)_q-$ in which q is the integer 2 or 3 and in which R^{cc} and R^{cd} are independently hydrogen or (1-3C)alkyl or the radical $R^{cc}R^{cd}N$ is pyrrolidino, piperidino or morpholino;

for a radical of formula Id, R^{da} is 1, 2 or 3;

for a radical of formula Ie, J^e is oxygen, sulfur or NR^{ea} in which R^{ea} is hydrogen or (1-3C)alkyl; R^{eb} is hydrogen, (1-6C)alkyl which may bear a hydroxy substituent and/or one to three fluoro substituents, (3-6C)alkenyl (in which a vinyl carbon is not bound to nitrogen), 2-hydroxyethyl, (3-7C)cyloalkyl, Ar or Het; R^{ec} is hydrogen, (1-6C)alkyl which may bear a hydroxy substituent and/or one to three fluoro substituents, (3-6C)cycloalkyl, (1-5C)alkoxy (only when J^e is oxygen), (3-6C)cycloalkoxy (only when J^e is oxygen), or an amino group of formula $NR^{ed}R^{ee}$ containing zero to seven carbon atoms in which each of R^{ed} and R^{ee} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{ed}R^{ee}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl group may bear a (1-3C)alkyl substituent at the 4-position);

for a radical of formula If, J^f is oxygen, sulfur or NR^{fa} in which R^{fa} is hydrogen or (1-3C)alkyl; L^f is a divalent hydrocarbon group in which the 1-position is bound to the carbon bearing the group J^f, the divalent group L^f being selected from trimethylene, cis-propenylene, tetramethylene, cis-butenylene, cis-but-3-enylene, cis,cis-butadienylene, pentamethylene and cis-pentenylene which divalent group L^f itself may bear one or two methyl substituents;

for a radical of formula Ig, Z^g is (1-8C)alkyl or (3-8C)cycloalkyl which may bear one or more substituents selected from the group consisting of halo, (3-6C)cycloalkyl, cyano,

nitro, hydroxy, (1-4C)alkoxy, (1-5C)alkanoyloxy, aroyl, heteroaroyl, oxo, imino (which may bear a (1-6C)alkyl, (3-6C)cycloalkyl, (1-5C)alkanoyl or aroyl substituent), hydroxyimino (which hydroxyimino may bear a (1-4C)alkyl or a phenyl substituent on the oxygen), an amino group of formula $NR^{ga}R^{gb}$, an amino group of formula $NR^{gc}R^{gd}$, an amidino group of formula $C(=NR^{gg})NR^{ge}R^{gf}$, and a carbamoyl group of formula $CON(OR^{gh})R^{gi}$, but excluding any radical wherein a hydroxy and an oxo substituent together form a carboxy group, wherein an amino group of formula $NR^{ga}R^{gb}$ contains zero to seven carbon atoms and each of R^{ga} and R^{gb} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{ga}R^{gb}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent group at the 4-position); and wherein R^{gc} is hydrogen or (1-3C)alkyl and R^{gd} is (1-5C)alkanoyl, aroyl or heteroaroyl; or R^{gd} is a group of formula $C(=J^g)NR^{ge}R^{gf}$ in which J^g is oxygen, sulfur, NR^{gg} or CHR^{gj}; and wherein the amino group $NR^{ge}R^{gf}$ contains zero to seven carbon atoms and each of R^{ge} and R^{gf} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{ge}R^{gf}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position) or R^{ge} is hydrogen or (1-4C)alkyl and R^{gf} together with R^{gg} forms an ethylene or trimethylene group; R^{gg} is hydrogen, (1-4C)alkyl or together with R^{gf} forms an ethylene or trimethylene group; R^{gj} is cyano, nitro or SO_2R^{gk} and R^{gk} is (1-4C)alkyl or phenyl; R^{gh} and R^{gi} are independently (1-3C)alkyl; and in which a cyclic group which is a substituent on Z^g or formed by substitution on Z^g may bear one or more (1-3C)alkyl groups on carbon as further substituents; and in which any aryl or heteroaryl group which is a part of the group Z^g may bear one or more halo, (1-4C)alkyl, (1-4C)alkoxy, cyano, trifluoromethyl or nitro substituents;

for a radical of formula Ih, G^h denotes a single bond, a double bond or a divalent hydrocarbon radical; J^h denotes a radical joined to the ring by a single bond if G^h denotes a double bond or, otherwise, a radical joined by a double bond; M^h denotes a heteroatom, a substituted heteroatom, or a single bond; and L^h denotes a hydrocarbon radical in which the 1-position is attached to M^h; wherein the values of G^h, J^h, M^h and L^h are selected from

(a) G^h is a single bond; J^h is oxo or thioxo: M^h is oxy, thio or NR^{ha}; and L^h is L^{ha};

(b) G^h is a single bond; J^h is NR^{hb}; M^h is NR^{ha}; and L^h is L^{ha};

(c) G^h is a double bond, J^h is OR^{ha}, SR^{ha} or $NR^{hc}R^{hd}$; M^h is nitrogen; and L^h is L^{ha};

(d) G^h is methylene which may bear one or two methyl substituents; J^h is oxo, thioxo or NR^{he}; M^h is oxy, thio, sulfinyl, sulfonyl or NR^{ha}; and L^h is L^{hb};

(e) G^h is a single bond; J^h is oxo, thioxo or NR^{he}; M^h is nitrogen; and L^h is L^{hc};

(f) G^h is methine, which may bear a (1-3C)alkyl substituent; J^h is oxo, thioxo or NR^{he}; M^h is nitrogen: and L^h is L^{hd};

(g) G^h is cis-vinylene, which may bear one or two methyl substituents; J^h is oxo, thioxo, or NR^{he}; M^h is nitrogen; and L^h is L^{he}; and

(h) G^h is a single bond; J^h is oxo or thioxo; M^h is a single bond; and L^h is L^{hf}; wherein

R^{ha} is hydrogen or (1-3C)alkyl; R^{hb} is hydrogen, (1-3C)alkyl, cyano, (1-3C)alkylsulfonyl or nitro; R^{hc} and R^{hd} are independently hydrogen or (1-3C)alkyl or the radical $NR^{hc}R^{hd}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{he} is hydrogen or (1-3C)alkyl; L^{ha} is ethylene, cis-vinylene, trimethylene or tetramethylene which radical L^{ha} itself may bear one or two methyl substituents; L^{hb} is ethylene or trimethylene which radical L^{hb} itself may bear one or two methyl substituents; L^{hc} is prop-2-en-1-yliden-3-yl, which radical L^{hc} itself may bear one or two methyl substituents; L^{hd} is cis-vinylene, which radical L^{hd} itself may bear one or two methyl substituents; L^{he} is methine, which radical L^{he} itself may bear a (1-3C)alkyl substituent; and L^{hf} is 4-oxabutan-1,4-diyl;

for a radical of formula Ij, X^j is (1-6C)alkyl, $-CH_2OR^{ja}$, $-CH_2SR^{ja}$, $-CH_2S(O)R^{jg}$, $-CH_2S(O)_2R^{jg}$, $-COR^{ja}$, $-COOR^{ja}$, $-C(=J^{ja})NR^{jb}R^{jc}$, $-C(R^{ja})(OR^{jd})(OR^{je})$, $-CH_2N(R^{ja})C(=J^{ja})R^{jf}$, $-CH_2N(R^{ja})COOR^{jg}$ or $-CH_2N(R^{ja})C(=J^{ja})NR^{jb}R^{jc}$;

B^j is a direct bond and L^j is a hydrocarbon chain in which the 1-position is bound to B^j and L^j is selected from trimethylene, tetramethylene, cis-1-butenylene and cis,cis-butadienylene; or B^j is $N(R^{jh})$ and L^j is a hydrocarbon chain selected from ethylene, trimethylene and cis-vinylene; or B^j is N and L^j is a hydrocarbon chain in which the 1-position is bound to B^j and L^j is cis,cis-prop-2-en-1-ylidin-3-yl; J^j and J^{ja} are independently oxygen or sulfur; R^{ja}, R^{jf} and R^{jh} are independently hydrogen or (1-6C)alkyl; R^{jb} and R^{jc} are independently hydrogen or (1-6C)alkyl; or the radical $NR^{jb}R^{jc}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{jd} and R^{je} are independently (1-3C)alkyl or together form a divalent hydrocarbon chain selected from ethylene and trimethylene; R^{jg} is (1-6C)alkyl; and

for a radical of formula Ik, Z^k is a nitrogen linked radical of formula II wherein E^1, E^2, E^3 and E^4 form a divalent four membered chain ($-E^1=E^2-E^3=E^4-$) in which each of E^1, E^2, E^3 and E^4 is methine; or in which one or two of E^1, E^2, E^3 and E^4 is nitrogen and the remaining E^1, E^2, E^3 and E^4 are methine; and further wherein one or more of E^1, E^2, E^3 and E^4 which is methine may bear a halo, (1-3C)alkyl, hydroxy, (1-3C)alkoxy, (1-3C)alkylthio, (1-3C)alkylsulfinyl or (1-3C)alkylsulfonyl substituent; and wherein the radicals F^k, G^k, and $I^k(X^k)$ are selected from

(a) G^k is a direct bond, $I^k(X^k)$ is a radical having the formula $=C(Z^k)-$ and F^k is a radical selected from $-CH=$ and $-N=$;

(b) G^k is a direct bond, $I^k(X^k)$ is a radical having the formula $-C(=J^k)-$ and F^k is a radical selected from $-N(R^{kf})-$, $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-N(R^{kf})-$ and $-CH=N-$;

(c) G^k is a radical having the formula $-CH_2-$, $I^k(X^k)$ is a radical having formula $-C(=J^k)-$ and F^k is selected from $-CH_2-$ and $-N(R^{kf})-$; and

(d) G^k is selected from $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$ and $-N=CH-$, $I^k(X^k)$ is a radical having the formula $-C(=J^k)-$ and F^k is a direct bond: wherein

J^k is oxygen or sulfur: Z^k is $-OR^{ka}$, $-SR^{ka}$, $-COR^{ka}$, $-COOR^{ka}$, $-C(=J^{ka})NR^{kb}R^{kc}$ or $-C(R^{ka})(OR^{kd})(OR^{ke})$; J^{ka} is oxygen or sulfur; R^{ka} and R^{kf} are independently hydrogen or (1-6C)alkyl; R^{kb} and R^{kc} are independently hydrogen or (1-6C)alkyl; or the radical $NR^{kb}R^{kc}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{kd} and R^{ke} are independently (1-3C)alkyl or R^{kd} and R^{ke} together form ethylene or trimethylene; or Z^k is an imido radical selected from phthalimido, succinimido, maleimido, glutarimido, and 3-oxa-, 3-thia- and 3-azaglutarimido, in which the imido radical may bear one or more (1-3C)alkyl substituents and, in addition, the aromatic portion of the phthalimido may bear one or more halo, hydroxy or (1-3C)alkoxy substituents: and wherein

for a radical Q^1, Ar is a phenyl radical or an ortho-fused bicyclic carbocyclic radical of nine of ten ring atoms in which at least one ring is aromatic, which radical Ar may be unsubstituted or may bear one or more substituents selected from halo, cyano, trifluoromethyl, (1-4C)alkyl, (1-4C)alkoxy, methylenedioxy, hydroxy, mercapto, $-S(O)_nR^{xa}$, (1-5C)alkanoyl, (1-5C)alkanoyloxy, nitro, $NR^{xb}R^{xc}$, $NR^{xd}R^{xe}$, $C(=NR^{xf})NR^{xg}R^{xh}$, $CONR^{xb}R^{xc}$ and $COOR^{xj}$ wherein n is the integer 0, 1, or 2; R^{xa} is (1-6C)alkyl, (3-6C)cycloalkyl or phenyl (which phenyl may bear a halo, trifluoromethyl, (1-3C)alkyl or (1-3C)alkoxy substitutent); the radical $NR^{xb}R^{xc}$ contains zero to seven carbons and each of R^{xb} and R^{xc} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{xb}R^{xc}$ is pyrrolidino, piperidino, morpholino, thiomorpholine (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); and wherein R^{xd} is hydrogen or (1-4C)alkyl and R^{xe} is (1-5C)alkanoyl, benzoyl; or a group of formula $C(=J^x)NR^{xg}R^{xh}$ in which J^x is oxygen, sulfur, NR^{xf} or CHR^{xi}; R^{xf} is hydrogen, (1-5C)alkyl or together with R^{xg} forms an ethylene or trimethylene diradical, the radical $NR^{xg}R^{xh}$ contains zero to 7 carbons and each of R^{xg} amd R^{xh} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{xg}R^{xh}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a

(1-3C)alkyl substituent at the 4-position); or R^{xg} together with R^{xf} forms an ethylene or trimethylene diradical and R^{xh} is hydrogen or (1-5C)alkyl; R^{xi} is cyano, nitro, (1-5C)alkylsulfonyl or phenylsulfonyl; and R^{xj} is hydrogen, (1-5C)alkyl or benzyl; and Het is a radical (or stable N-oxide thereof) attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms selected from oxygen, sulfur and nitrogen, or an ortho-fused bicyclic heterocycle derived therefrom by fusing a propenylene, trimethylene, tetramethylene or benz-diradical, which radical Het may be unsubstituted or may be substituted on carbon by one or more of the substituents defined above for Ar and may be substituted on nitrogen by (1-3C)alkyl;

Q^2 is phenyl which may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl and methylenedioxy; or Q^2 is thienyl, imidazolyl, benzo[b]thiophenyl or naphthyl any of which may bear a halo substituent; or Q^2 is biphenylyl; or Q^2 is carbon-linked indolyl which may bear a benzyl substituent at the 1-position;

Q^3 is hydrogen, or (1-4C)alkyl; and

Q^4 is $-OR^2$ or $-NR^3R^4$; wherein

R^2 is hydrogen, (1-6C)alkyl, (3-7C)cycloalkyl, aryl(1-3C)alkyl or heteroaryl(1-3C)alkyl, wherein an aryl or heteroaryl group may bear one, two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-S(=O)_2NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, and methylenedioxy, and further wherein any arylethyl, arylpropyl, heteroarylethyl or heteroarylpropyl group may optionally be substituted at the position a to the aryl or heteroaryl group by a group selected from oxo, and $=NOR^{11}$;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl, (3-7C)cycloalkyl, aryl, heteroaryl, aryl(1-3C)alkyl and heteroaryl(1-3C)alkyl, wherein any aryl or heteroaryl group may bear one two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-S(=O)_2NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, and methylenedioxy, and further wherein any arylethyl, arylpropyl,

heteroarylethyl or heteroarylpropyl group may optionally be substituted at the position a to the aryl or heteroaryl group by a group selected from oxo, and $=NOR^{11}$; or

$-NR^3R^4$ taken together represents a cyclic amino radical selected from pyrrolidinyl, piperidino, 1,2,3,6-tetrahydropyridyl, 1,2,3,4-tetrahydroquinolyl, and 1,2,3,4-tetrahydroisoquinolyl, which cyclic amino radical may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-S(=O)^2NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, phenyl, acetamidomethyl, and methylenedioxy; and

R^5-R^{11} are independently selected from hydrogen and (1-3C)alkyl

or the N-oxide of the nitrogen in Q^1 indicated by Δ in formulae Ia-Ik (or of either basic piperazinyl nitrogen of Q^1 when Z^a is nitrogen);

or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the nitrogen in Q^1 indicated by Δ in formulae Ia-Ik (or either basic piperazinyl nitrogen of Q^1 when Z^a is nitrogen) is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R^1 is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

3. A compound as claimed in claim 1 wherein:

Q^1 is 4-hydroxy-4-phenylpiperidino, 4-acetamido-4-phenylpiperidino, 4-(2-methylsulfinylphenyl)piperidino, 4-(2-oxopiperidino)piperidino, or 4-(2-oxoperhydropyrimidin-1-yl)piperidino;

Q^2 is phenyl which may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl and methylenedioxy; or Q^2 is thienyl, imidazolyl, benzo[b]thiophenyl or naphthyl any of which may bear a halo substituent; or Q^2 is biphenylyl; or Q^2 is carbon-linked indolyl which may bear a benzyl substituent at the 1-position;

Q^3 is hydrogen; and

Q^4 is $-OR^2$ or $-NR^3R^4$; wherein

R^2 is hydrogen, (1-6C)alkyl, (3-7C)cycloalkyl, aryl(1-3C)alkyl or heteroaryl(1-3C)alkyl, wherein an aryl or heteroaryl group may bear one, two or three

substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-S(=O)_2NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, and methylenedioxy;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl, (3-7C)cycloalkyl, aryl, heteroaryl, aryl(1-3C)alkyl and heteroaryl(1-3C)alkyl, wherein any aryl or heteroaryl group may bear one two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-S(=O)_2NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, and methylenedioxy; or

the group $-NR^3R^4$ taken together represents a cyclic amino radical selected from pyrrolidinyl, piperidino, 1,2,3,6-tetrahydro-pyridyl, 1,2,3,4-tetrahydroquinolyl, and 1,2,3,4-tetrahydroiso-quinolyl, which cyclic amino radical may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-S(=O)_2NR^5R^6$, $-NR^7R^8$, $C(=O)NR^9R^{10}$, phenyl, acetamidomethyl, and methylenedioxy; and

R^5-R^{11} are independently selected from hydrogen and (1-3C)alkyl;

or the N-oxide of the nitrogen in Q^1;

or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the nitrogen in Q^1 is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R^1 is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

4. A compound as claimed in claim 1 wherein:

Ar is phenyl which may be unsubstituted or may bear a chloro, methyl, methoxy, hydroxy or methylsulfinyl substituent; Het is furyl, thienyl, 2-imidazolyl, 1,3,4-oxadiazol-2-yl, pyridyl or pyrimidinyl which ring may be unsubstituted or may bear a chloro, methyl, methoxy, hydroxy, methylsulfinyl, methoxycarbonyl or ethoxycarbonyl substituent; aryl is phenyl; heteroaryl is furyl, pyridyl, imidazolyl, indolyl or pyrimidinyl; halo is chloro or bromo; (1-3C)alkyl is methyl, ethyl, propyl or isopropyl; (1-4C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl; (1-5C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl or isopentyl; (1-6C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl or isohexyl; (1-8C)alkyl is

methyl, ethyl, propyl, isopropyl, isopentyl, 1-ethylpropyl, hexyl, isohexyl, 1-propylbutyl, or octyl; (3-6C)cycloalkyl is cyclopropyl, cyclopentyl or cyclohexyl; (3-7C)cycloalkyl is cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl; (3-8C)cycloalkyl is cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; (3-6C)alkenyl is allyl, 2-butenyl or 3-methyl-2-butenyl; (1-4C)alkanoyl is formyl, acetyl, propionyl, butyryl or isobutyryl; and (1-5C)alkanoyl is formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl or pivaloyl.

5. A compound as claimed in claim 1 wherein: Ar is phenyl which may be unsubstituted or may bear a methoxy or hydroxy substituent; Het is pyridyl or pyrimidinyl which ring may be unsubstituted or may bear a methoxy, hydroxy or methylsulfinyl substituent; heteroaryl is pyridyl; halo is chloro; (1-3C)alkyl is methyl; (1-4C)alkyl is methyl or ethyl; (1-5C)alkyl is methyl, ethyl, propyl or isopropyl; (1-6C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or *t*-butyl; (1-8C)alkyl is methyl, ethyl, propyl, isopropyl, 1-ethylpropyl or 1-propylbutyl; (3-6C)cylcoalkyl is cyclopropyl or cyclopentyl; (3-7C)cycloalkyl is cyclopropyl or cyclopentyl; (3-8C)cycloalkyl is cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl; (3-6C)alkenyl is allyl; (1-4C)alkanoyl is formyl or acetyl; and (1-5C)alkanoyl is formyl, acetyl, propionyl, butyryl or isobutyryl.

6. A compound as claimed in claim 1 wherein: Q^1 is 4-hydroxy-4-phenylpiperidino, 4-acetamido-4-phenylpiperidino, 4-(2-methylsulfinylphenyl)piperidino, 4-(2-oxopiperidino)piperidino, or 4-(2-oxoperhydropyrimidin-1-yl)piperidino; Q^2 is 3,4-dichlorophenyl, or 3,4-methylenedioxyphenyl; Q^3 is hydrogen; and Q^4 is benzylamino, 4-phenylpiperidino, 4-methoxybenzylamino, cyclohexylamino, 4-methylbenzylamino, (benzyl)(methyl)amino, (methyl)(phenyl)amino, phenylamino, benzyloxy, (2-methoxybenzyl)-(methyl)amino, [3,5-bis(trifluoromethyl)benzyl](methyl)amino, 2-methoxybenzylamino, ethoxy, (3,5-dichloro-2-methoxybenzyl)amino, N-[3,5-dichloro-2-methoxybenzyl]-N-methylamino, a radical of formula VII wherein E is oxy and m is 1; a radical of formula VII wherein E is oxy and m is 2; or 3,5-bis(trifluoromethyl)benzylamino.

7. A compound as claimed in claim 1 wherein Q1 is a radical of formula Ie, If, Ig, Ih, Ij or Ik..

8. A compound as claimed in claim 1 wherein Q^1 is a radical of formulae Ic, Id, Ie, If, Ig, Ih, Ij , Ik Im, In, Ip, Iu, Iv, Iw, or Ix as defined in claim 1, or Q^1 is a radical of formula Ib wherein Z^b is a substituted imino group $R^{ba}N$ or $R^{ba}CH_2N$ in which R^{ba} is (3-7C)cycloakyl, Ar, Het, Ar(carbonyl), Het(carbonyl), CH_2 $NR^{be}R^{bf}$, $C(=O)NR^{be}R^{bf}$, $CH_2C(=O)NR^{be}R^{bf}$; or Z^b is a disubstituted methylene group $R^{bb}(CH_2)_p$-C-R^{bc} in which R^{bb} is Ar or Het; p is the integer 0 or 1; and R^{bc} is hydrogen, hydroxy, (1-4C)alkoxy, (1-4C)alkanoyloxy, $COOR^{bd}$ (wherein R^{bd} is hydrogen or (1-3C)alkyl), cyano, CH_2 $NR^{be}R^{bf}$, $C(=O)NR^{be}R^{bf}$, $NR^{be}R^{bf}$ or SR^{bg} in which R^{be} and R^{bf} are independently hydrogen, (1-4C)alkyl, (1-4C)hydroxyalkyl or (1-4C)alkanoyl, or the radical $NR^{be}R^{bf}$ is pyrrolidino, piperidino or morpholino; and R^{bg} is hydrogen or (1-4C)alkyl.

9. A pharmaceutical composition comprising a compound of formula I;

or the N-oxide of the nitrogen in Q^1 indicated by Δ in formulae Ia-Ix (or of either basic piperazinyl nitrogen of Q^1 when Z^a is nitrogen);

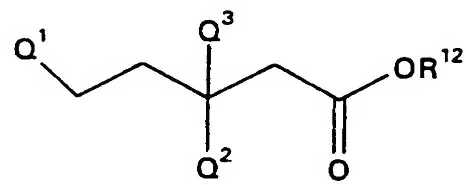
or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the nitrogen in Q^1 indicated by Δ in formulae Ia-Ix (or either basic piperazinyl nitrogen of Q^1 when Z^a is nitrogen) is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R^1 is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion; as defined in any one of claims 1-8; and a pharmaceutically acceptable diluent or carrier.

10. A process for the manufacture of a compound of formula I: or the N-oxide of the nitrogen in Q^1; or a pharmaceutically acceptable salt thereof; or a quaternary ammonium salt thereof in which the nitrogen in Q^1 is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R^1 is (1-4C)alkyl or benzyl and the associated counterion A is a

pharmaceutically acceptable anion; as defined in any one of claimes 1-8, which is characterized by:

(a) Acylating an amine of formula $-NR^3R^4$, with an ester of formula IV:

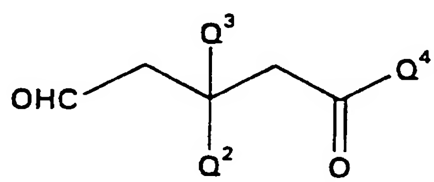


IV

wherein R^{12} is a suitable alkyl radical such as for example (1-3C)alkyl;

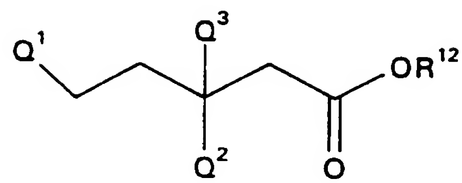
(b) For an acid addition salt of a compound of formula I, treating a corresponding compound of formula I which is in the free-base form, with an acid

(c) Alkylating an amine of formula Q^1-H with an aldehyde of formula V:



by reductive alkylation;

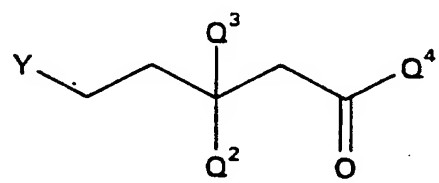
(d) Acylating an amine of formula $-NR^3R^4$, with an acid of formula IV:



IV

wherein R^{12} is a hydrogen:

(e) Alkylating an amine of formula Q^1-H with an alkylating agent of formula VI:



VI

in which Y is a conventional leaving group;

(f) For an N-oxide of the nitrogen in Q^1 indicated by Δ in formulae Ia-Ix (or of either basic piperazinyl nitrogen of Q^1 when Z^a is nitrogen); oxidizing the nitrogen of a corresponding compound of formula I using a conventional procedure;

(g) For a quaternary ammonium salt of the nitrogen in Q^1 indicated by Δ in formulae Ia-Ix (or either basic piperazinyl nitrogen of Q^1 when Z^a is nitrogen), alkylating the nitrogen in a corresponding compound of formula I with an alkylating agent of formula R^1Y wherein Y is a leaving group;

(h) For a compound of formula I which bears a sulfinyl group, oxidizing the sulfur of a corresponding compound of formula I which bears a sulfide group;

(i) For a compound of formula I which bears a sulfonyl group, oxidizing a sulfide or sulfinyl group of a corresponding compound of formula I; and

(j) For a compound of formula I which bears an aromatic hydroxy group, cleaving the ether of a corresponding compound of formula I which bears an aromatic alkoxy group.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/00259

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/52 C07D211/58 C07D401/06 C07D409/12 A61K31/445
C07D401/12 C07D405/12 C07D401/04 C07D471/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 29309 (MERCK) 22 December 1994 see the whole document see in particular: Spiro[3H-indole-3,4'-piperidine]-1'-pentanamide, .beta.-(3,4-dichlorophenyl)-1,2-dihydro-N-methoxy-N-methyl-1-(methylsulfonyl)-,(R) RN 167485-71-4 ---	1-10
A,P	US,A,5 434 158 (S. K. SHAH) 18 July 1995 see the whole document ---	1-10
A	FR,A,2 100 711 (JANSSEN) 24 March 1972 see the whole document -----	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 April 1996	29.05.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Kissler, B

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 96/00259

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9429309	22-12-94	AU-B-	7201194	03-01-95
		CA-A-	2163995	22-12-94
		EP-A-	0702681	27-03-96
		ZA-A-	9403946	20-01-95
US-A-5434158	18-07-95	AU-B-	2391595	16-11-95
		WO-A-	9528931	02-11-95
FR-A-2100711	24-03-72	AT-A,B	312606	15-12-73
		BE-A-	767798	29-11-71
		CH-A-	549015	15-05-74
		CH-A-	553182	30-08-74
		DE-A-	2126559	05-10-72
		DE-C-	2167193	19-05-83
		GB-A-	1319040	31-05-73
		JP-C-	1242513	26-11-84
		JP-A-	55120576	17-09-80
		JP-B-	59014467	04-04-84
		JP-C-	1258821	12-04-85
		JP-A-	55120577	17-09-80
		JP-B-	59036991	06-09-84
		JP-C-	1182918	27-12-83
		JP-A-	56127355	06-10-81
		JP-B-	58017749	09-04-83
		NL-A-	7106829	03-12-71
		SE-B-	369418	26-08-74
		US-A-	3714159	30-01-73
		US-A-	3884916	20-05-75